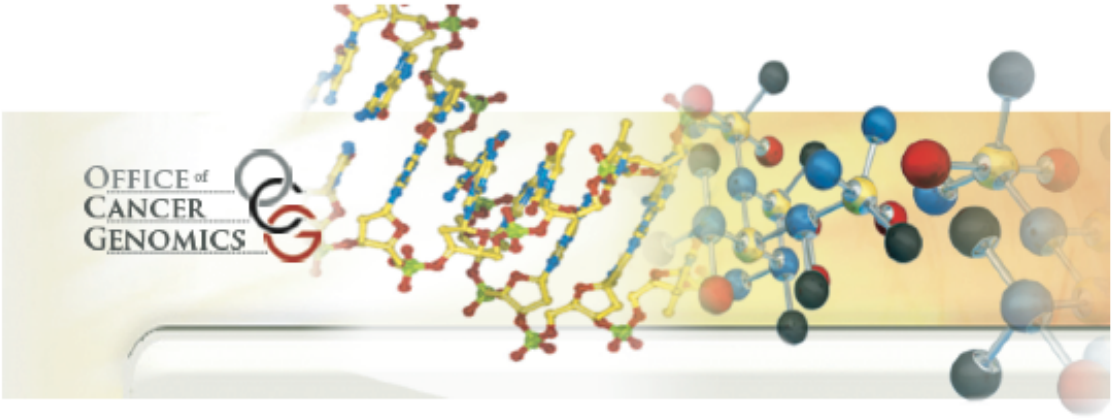
National Cancer Institute



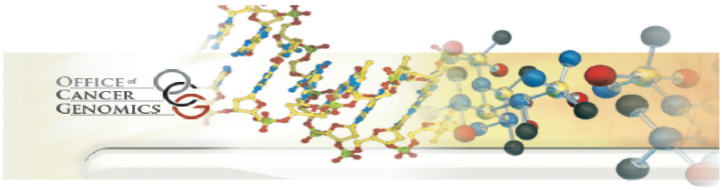
OCG TUMOR MOLECULAR CHARACTERIZATION PROJECTS

STANDARD OPERATING PROCEDURES MANUAL

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

HIV+ Tumor Molecular Characterization Project
Standard Operating Procedures Manual



Dear Colleague,

You are about to review the latest version of the National Cancer Institute Office of Cancer Genomics book of Standard Operating Protocols (SOPs) that should be followed when you contribute samples and data to our large-scale genomic characterization project(s).

The sample and data acquisition process is explained in comprehensive detail to ensure that all materials contributed will be of sufficient quality to be utilized in the projects. However, the actual process is simple and requires only six basic steps:

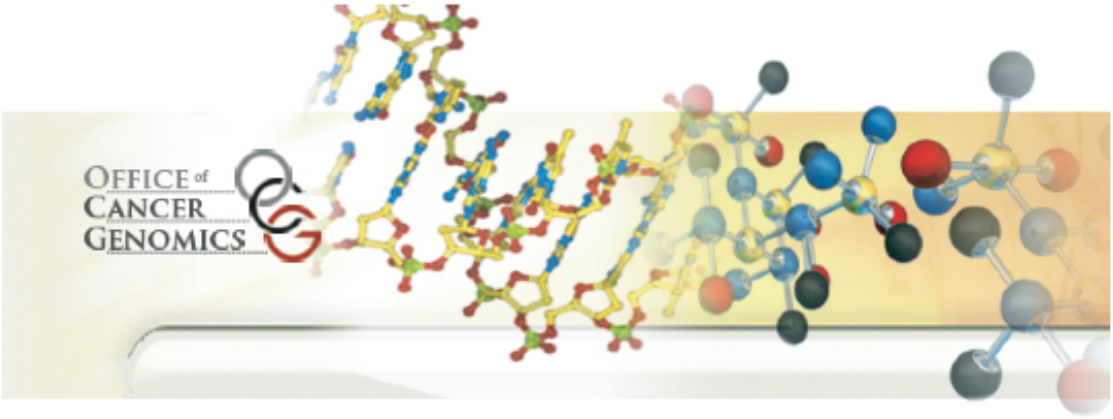
1. Creation of an IRB approved protocol and informed consent forms.
2. Institutional Certification of patient consent.
3. Acquisition and freezing of tumor samples.
4. Acquisition and freezing of patient-matched normal samples (e.g., blood).
5. Acquisition of unstained formalin-fixed paraffin-embedded sections for pathology review.
6. Shipment of tissues and data.

The book is divided into general protocols and templates that apply to all projects, as well as tissue/disease specific ones. Although many protocols are included in this book, only a handful of them may apply to yourself, depending on your role in the acquisition process :

- Clinical Practitioners:
  - IRB approved protocol and informed consent templates.
  - General guidelines on the process and clinical data requirements (SOP#101).
- Institutions:
  - Institutional certification letter.
  - Material Transfer Agreement (MTA) template and instructions on how to fill it (SOP#109).
- Laboratory or research personnel:
  - General guidelines on the process and clinical data requirements (SOP#101).
  - Processing tissue for molecular characterization (SOP#102).
  - Processing blood samples (SOP#103).
  - Shipping frozen biosamples in cryoports (SOP#104) and FFPE slides for pathology review (SOP#107)

Should you require any clarification on the protocols and/or process, please do not hesitate to contact the appropriate OCG personnel listed in your SOPs

National Cancer Institute



General Clinical Templates

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

LAB PROTOCOL FOR CONSENTING THE LIVING PATIENTS FOR

[Project Name] PROJECT

TABLE OF CONTENTS

Template

OFFICE OF CANCER GENOMICS SUGGESTED LANGUAGE FOR

IRB PROTOCOL FOR (RE)-CONSENTING THE LIVING PATIENTS FOR [Project Name] PROJECT

Protocol Body

1.0 Objectives

To obtain consent from all living patients for the use of their samples and associated annotation, in the tumor bank retrospective collections, to perform genetic and proteomic analyses. The genetic analyses will be performed by **[Project Name]** project, a network of collaborating institutions sponsored by the National Cancer Institute (NCI).

2.0 Rationale
2.1 Purpose of the Project

The purpose of the **[Project Name]** project is to discover somatic genetic changes associated with cancer to lead to better ways to prevent, detect, and treat cancer. The data generated may be used to study other diseases as well.

The **[Project Name]** project is designed to identify most of the somatic genetic changes that can cause cancer in people. Therefore, **[Project Name]** project would like to study the genetic material from the retrospective collections of cancer tissue, in which statistically powerful sample numbers have already been collected; as well as prospectively collected cases. The genetic material (DNA, RNA) from the cancer tissue will be compared to germline genetic material from the normal tissue and/or blood to find the differences that exist. By combining the genetic information with clinical information it may be possible to identify the genetic changes that are associated with a particular type of cancer. This same process of analysis will be repeated with many (hundreds of) samples for this research project. By studying many **[Cancer Type]** cancers in this way, **[Project Name]** project expects to identify most of the genetic changes associated with this **(these)** kind**(s)** of cancer. Since **[Project Name]** project also will combine genetic information with information from medical records, such as the tissue pathology and responses of different cancers to different treatments, this project could lead to more knowledge about why certain cancers respond differently to treatments. With such knowledge, future treatments potentially could become customized to a patient's unique genetic make-up.

3.0 Description of the Research
3.1 Eligibility of Subjects
3.2 Collection of Samples and Medical Information

Patients who had diagnosis of **[Cancer Type]** cancer and underwent surgery from which stores/banked tissue is available along with matching blood and normal solid tissue. In total, for **[Project Name]** project, **[Sample Number]** successful analyses must be completed per cancer to yield the expected sensitivity toward detecting somatic genetic changes. Given that a certain percentage of samples do not successfully yield analytes (RNA and DNA), it is expected that between **[Sample Number]** and **[Sample Number]** samples will be needed by **[Project Name]**.

Template

About **[Sample Number]** of that number of patient samples along with matching blood and normal solid tissue will be collected from **[Institution Name]**; however, depending on the contributions by other clinical sites, the number could be higher.

Sample amount requirement specifications:
- **[Tumor mass]** mg of solid tumor
- **[Blood Volume]** ml (or enough to obtain 50 ug of germline DNA) of matching blood
- **[Tissue Mass]** mg of solid normal tissue (or enough to obtain 50 ug of germline DNA)

Specifically, this protocol requests:
- Permission to obtain solid tumor tissues donated by the patient at the time of the surgery.
- If a second type of normal tissue (blood) was collected before or after the surgery, we seek permission to receive some of this blood and genetic material that already may have been extracted from this blood.
- If an adequate blood sample is not available for this project, permission to collect a sample by drawing about 4 tablespoons of blood from a vein. If the patient objects to having blood drawn, we will ask to collect normal tissue by swabbing cells from the inside of their cheeks.
- Permission to collect information from the patient medical records, including age, ethnic background, diagnosis, disease history, medical treatments, and response to treatments.

3.3 Coding of Tissue Samples and Medical Information

Tissues, blood sample, and medical information will be labeled with a code.
Only the PI and/or the specified collaborator (co-PI) for **[Cancer Type]** cancers at **[Institution Name]** will have the information that matches the code to traditionally-used identifying information, such as the patient name, address, phone number, medical record number, or social security number. PI/co-PI will keep the information that matches the code to this traditionally-used identifying information in a safeguarded database at **[Institution Name]**. Only authorized people, who have specifically agreed to protect patient identity, will have access to this database. All materials conveyed to the **[Project Name]** will be labeled with a project-assigned ID, removing traditionally-used identifying information, such as your name, address, phone number, or social security number. All other researchers and personnel, including those who will be working with the patient samples and medical information, will not have access to any of the traditionally used identifying information about the patient.

3.4 Storage and Release of Samples and Medical Information

Coded tissue samples will be sent to an NCI-sponsored storage facility, designated for the **[Project Name]** project. The samples will be processed there and portions of the molecular analytes extracted from samples then will be sent to different types of laboratories as part of this project. The remaining portions of the samples will be stored at the storage facility for an unlimited period of time for future use in research related to cancer or, perhaps, in other research projects. At the end of the project, remaining samples will be disposed of or returned in accordance with the requests of **[Institution Name]**.

Coded clinical data will be sent for reformatting into data structures compliant with standards developed by the NCI cancer Biomedical Informatics Grid (caBIG) standards. That data will then be deposited into a central **[Project Name]** project database, where it will be integrated with the molecular profiling data generated with the DNA and RNA. Only data stripped of identifiers, in compliance with the definition specified in the HIPAA Limited Data Set definition, will be sent

Template

from **[Institution Name]**.

4.0 Research Plan and Methods

Laboratories designated by **[Project Name]** project can analyze DNA and RNA by Single Nucleotide Polymorphism (SNP) analysis, gene copy number analysis, loss of heterozygosity, DNA methylation, mRNA expression profiling, micro RNA expression profiling, genomic sequencing, transcriptome sequencing, micro RNA sequencing, histone modification assays and/or chromatin immunoprecipitation methods. In addition, proteomic analysis can be obtained by complementary protein (using Reverse Phase Protein Arrays - RPPA), and tissue information (Tissue microarrays – TMA) to match with the DNA/RNA information.

4.1 Data

- Information (data) from analyses of the coded samples and the coded medical information will be put into databases along with information from the other research participants. These databases will be accessible by the Internet.
- Coded medical information and information from more detailed analyses of the coded samples will be put in a controlled-access database. The information in this database will be available only to researchers and institutions who have received approval from an NIH Data Access Committee after certifying their adherence to patient data protection policies for the project.
- Anonymous information from the analyses will be put in a completely public database, available to anyone on the Internet.
- *Traditionally-used identifying information about the patient, such as name, address, telephone number, or social security number, will NOT be put into either the public or controlled-access databases for this project.*

5.0 Recontact

In the future, we may want to obtain additional samples or follow-up information about the patient health or medical care. Should this be needed, this protocol seek permission for a person from **[Institution Name]** to contact the patient to ask whether the patient would be interested in participating in this additional research.

6.0 Financial Compensation/Costs

Patients will not be paid to participate in this project. Tissue samples and the medical information will be used only for research purposes and will not be sold. It is possible that some of the research conducted using the samples or information eventually will lead to the development of new diagnostic tests, new drugs or other commercial products. Should this occur, the patient will not receive any part of the profits generated from such products.

The patient will not incur any expenses from participating in this project.

The chance that the patient will be physically injured as a result of participating in this project is very small. However, if the patient is physically injured as a result of participating in this project, emergency medical treatment for the patient's research-related injury will be provided to the patient at no cost.

Template

7.0 Potential Benefits of Participating in the Project

The patient should not expect to personally benefit from this research. The main reason the patient may want to participate is to help researchers and health professionals around the world to better understand the causes of cancer and other diseases so that they can find better ways to prevent, detect, treat, and cure such illnesses. We hope that the participant will feel good knowing that they may be helping future patients with cancer or with other diseases.

7.1 Potential Risks of Participating in the Project
7.2 Physical Risks

- If a blood sample is NOT taken, there are no physical risks associated with this project.
- If a blood sample is taken, there are very few physical risks. Possible side effects from drawing the blood sample include mild pain, bleeding, bruising, and infection at the site of the needle insertion. Fainting or light-headedness can sometimes occur, but usually last only a few minutes.

7.3 Psychological or Social Risks Associated with Loss of Privacy

Patient privacy is very important to us and we will use many safety measures to protect their privacy. However, in spite of all of the safety measure that we will use, we cannot guarantee that the identity of the patient will never become known. Although the genetic information is unique to the patient, he/she does share some genetic information with their children, parents, brothers, sisters, and other relatives. Consequently, it may be possible that genetic information from them could be used to help identify the patient. Similarly, it may be possible that genetic information from the patient could be used to help identify the relatives.

While neither the public nor the controlled-access databases developed for this project will contain information that is traditionally used to identify the patient, such as the patient name, address, telephone number, or social security number, people may develop ways in the future that would allow someone to link the patient genetic or medical information in **[Project Name]** databases back to the patient. For example, someone could compare information in our databases with information from the patient (or a relative) in another database and be able to identify the patient (or the patient's relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking patient's genetic and medical information to the patient.

Since some genetic variations can help to predict the future health problems of the patient and the patient's relatives, this information might be of interest to employers, health providers, insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her relatives. Therefore, the patient genetic information potentially could be used in ways that could cause the patient or his/her family distress, such as by revealing that the patient (or a relative) carries a genetic disease or by leading to the denial of employment or insurance for the patient (or a relative).

There also may be other privacy risks that we have not foreseen. While we believe that the risks to the patient and his/her family are very low, we are unable to tell exactly what all of the risks are. There are some state laws that protect against genetic discrimination by employers or insurance companies, but there is no federal law yet that prohibits such discrimination. We believe that the benefits of learning more about cancer and other diseases outweigh these

Template

potential risks.

8.0 Confidentiality

We will make every attempt to protect the patient's confidentiality and to make sure that the patient's personal identity does not become known. The signed consent form will be stored in a locked file that will be accessible only to a very small number of authorized people involved in this project. We will carefully follow the coding, storage, and release plan explained in the *Description of the Research* section on pages 1-3 of this document.
To help us protect the confidentiality of the patient's information, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, we cannot be forced to disclose information that may identify the patient, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. We will use this Certificate to resist any demands for information that would identify the patient, with the following exceptions:

- The Certificate cannot be used to resist a request for the patient information from the United States Government when the information is to be used for auditing or evaluation of federally funded projects or for information that must be disclosed to meet the requirements of the federal Food and Drug Administration (FDA).
- The Certificate does not prevent the patient or a member of patient's family from voluntarily releasing information about the patient or patient's involvement in this research. Also, if the patient have given written consent to an insurer, employer, or other person to receive research information, then we may not use the Certificate to withhold that information.

9.0 Project Results

Individual results from this research project will not be given back to the patient or put into the patient's medical records. If research from this project is published in professional journals, there will be no traditionally-used identifying information, such as the patient's name, address, telephone number, or social security number, included in the publications. Some publications from this project will be found at the **[Project Website]** website.

10.0 Alternatives to Participating in the Project

The alternative option is not to participate.

Template

10.1 Voluntary Participation

The choice to participate in this research by consenting the use the patient's donated tissues and medical information for the **[Project Name]** project is completely up to the patient. **No matter what the patient decides to do, his/her decision will not affect their medical care**.

10.2 Withdrawal from the Project

Once coded DNA and RNA samples have been distributed to the participating research centers, and once the molecular analysis and patient information have been transferred to the central project databases, it will not be possible to destroy those data or samples. Unused tissue samples will be destroyed or returned to **[Institution Name]** per request, and codes linking the sample identifiers back to patient identities at **[Institution Name]** will be destroyed.

11.0 Contact Information

If they have any questions about the project or their participation, they would contact:

11.1 Principal Investigator:

[Researcher Name] at **[Researcher e-mail]**, **[Researcher phone]**.

11. 2 Co-Principal Investigator(s):

[Researcher Name] at **[Researcher e-mail]**, **[Researcher phone]**.
[Researcher Name] at **[Researcher e-mail]**, **[Researcher phone]**.

11.3 Other contact:

[Researcher Name] at **[Researcher e-mail]**, **[Researcher phone]**.

Template

NOTE: Highlighted text of this document has to be used as provided in your Institution's informed consent forms for the samples to be acceptable to the project

OFFICE OF CANCER GENOMICS SUGGESTED LANGUAGE FOR PROSPECTIVE TISSUE COLLECTIONS IN GENOMIC-SCALE PROJECTS

Purpose of the Project

We would like to invite you to participate in a research project called **[Project Name]**. The purpose of the **[Project Name]** project is to discover genetic changes associated with cancer, thus potentially leading to better prevention, detection and treatment of cancer, and perhaps other diseases as well.
This project is being sponsored by the National Cancer Institute (NCI), part of the government agency known as the National Institutes of Health (NIH).

Bodily tissues are made up of cells containing DNA, which is part of the unique genetic material carrying the instructions for your body's development and function. Cancer can result from changes in this genetic material, thereby causing cells to divide in an uncontrolled way and possibly to travel to other organs. Some of the genetic changes leading to cancer are currently known, however many remain to be discovered.

The **[Project Name]** project is designed to identify genetic changes that can cause cancer in humans. As such, we would like to study the genetic material obtained from your tumor tissue as part of the **[Project Name]**. We will compare the genetic material from your cancerous tissue with the genetic material from your normal tissue to find any differences that may exist. By combining information about genetic differences between normal and disease tissues along with information contained in your medical records, it may be possible to identify the genetic changes that are associated with your particular type of cancer. This same process will be performed with normal and cancerous tissues obtained from a number of other people who have agreed to participate in this research project. In this way, we expect to identify most of the genetic changes associated with many different kinds of cancer. By comparing treatment responses of patients with various cancers (through recorded medical information), this project could also lead to more knowledge about why certain cancers respond differently to treatments. With such knowledge, future treatment options could potentially become customized to a patient's unique genetic make-up.

Description of the Research

Collection of Samples and Medical Information

- Your scheduled surgery is part of the medical treatment that you agreed upon with your doctor. During surgery, cancerous tissue will be removed. Usually, when cancerous tissue is removed, very small amounts of nearby normal tissue are removed as well. Your surgery is not part of the **[Project Name]** research project. We will receive some of these cancerous and normal tissues following your

Template

surgery.
- We will collect a sample of blood (approximately 4 tablespoons), drawn from a vein in your arm, as a second type of normal tissue.
- Should you object to having blood drawn, we will instead swab cells from inside of your mouth through gentle sweeping of the inner cheeks to obtain a secondary source of normal tissue.
- We will also collect information from your medical records, including your age, ethnic background, diagnosis, disease history, medical treatments, and response to treatments.

Coding of Tissue Samples and Medical Information
- Your tissues, blood or buccal (cheek swab) sample, and medical information will be labeled with a confidential project-assigned ID.
- Only Dr. **[Physician Name]** at **[Institution Name]** will have the information that matches the code to traditionally-used identifying information, such as your name, address, phone number, or social security number. Dr. **[Physician Name]** will keep the information that matches the confidential code to this identifying information in a safeguarded database. Only authorized personnel, who have specifically agreed to protect your identity, will have access to this database. All materials conveyed to the **[Project Name]** will be labeled with a project-assigned ID, removing traditionally-used identifying information, such as your name, address, phone number, or social security number. All other researchers and personnel, including those who will be working with your samples and medical information, will not have access to any of the traditionally-used identifying information about you.

Storage and Release of Samples and Medical Information
- Your coded tissue samples will be sent to an NCI-sponsored storage facility. The facility will process the samples and then send portions of your samples to different types of laboratories for analysis as part of this project. One type of laboratory will analyze your DNA by a method called sequencing. Other laboratories will study your samples by different methods. The remaining tissue from your samples might be stored for an unlimited period of time for use in future research related to cancer, or perhaps in other research projects.
- Information obtained from analyses performed on your coded samples and medical information will be entered into Internet-accessible databases along with information acquired from the other research participants in this project.
    - Anonymous information from the analyses, which cannot be traced to any individual patient, will be available to anyone in a completely public Internet database.
    - Information obtained from more detailed analyses, along with your confidential coded medical information, will be put into a controlled-access database. The information in this database will be available only to researchers who have received approval from an NIH Data Access Committee. In gaining access to such information, researchers have to agree to use the data only for research projects and not to ever try to use it

Template

in order to identify the donor of the material. However, despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known.

Please note that traditionally-used identifying information about you, such as your name, address, telephone number, or social security number, will NOT be put into either the public or controlled-access databases for this project.

Recontact

- In the future, we may want to obtain additional samples or follow-up information about your health or medical care. Should this be needed, a person from **[Institution Name]** will contact you with an explanation of the reasons for any follow-up and to ask whether you would be interested in participating in this additional research.

Financial Compensation/Costs

You will not be paid to participate in this project. Your tissue samples and your medical information will be used for research purposes only and will not be sold. It is possible that some of the research conducted using your tissue samples or medical information will eventually lead to the development of new diagnostic tests, drugs or other commercial products. Should this occur, you will not receive any part of the profits generated from such products.

You will not incur any expenses from participating in this project. The chance that you will be physically injured as a result of participating in this project is highly unlikely. However, if you are physically injured as a result of participating in this project, emergency medical treatment for your research-related injury will be provided to you at no cost.

Potential Benefits of Participating in the Project

You should not expect to personally benefit from this research, aside from the knowledge that your participation will help researchers and health professionals around the world to better understand the causes of cancer and other diseases. Research projects such as this lead to better ways to prevent, detect, treat, and cure such illnesses.

Potential Risks of Participating in the Project

Physical Risks

- There are very few physical risks associated with this project. Possible side effects from drawing the blood sample include mild pain, bleeding, bruising, and infection at the site of the needle insertion. Fainting or light-headedness can sometimes occur, but usually lasts only a few minutes. Every precaution will be taken to minimize these effects.

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Psychological or Social Risks Associated with Loss of Privacy

- Your privacy is very important to us, and we use many safety measures to protect your privacy. However, despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.
- While neither the public nor the controlled-access databases developed for this project will contain information that is traditionally used to identify you (your name, address, telephone number, or social security number), technology may be developed in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a relative) in another database and be able to identify you (or your relative). It is also possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information back to you. Because some genetic variations can help to predict the current or future health problems of you and your relatives, this information may be of interest to employers, health providers, insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her relatives. Therefore, your genetic information could potentially be used in ways that could cause you or your family distress, such as by revealing that you (or a relative) carry a genetic disease or by leading to the denial of employment or insurance for you (or a relative).
- There also may be other privacy risks that we have not foreseen.

While we believe that the risks to you and your family are very low, we are unable to tell you exactly what all of the risks are. There are some state laws that protect against genetic discrimination by employers or insurance companies, but there is currently no federal law that prohibits such discrimination. We believe that the benefits of learning more about cancer and other diseases outweigh these potential risks.

Confidentiality

We will make every attempt to protect your confidentiality and to ensure that your personal identity remains anonymous. This signed consent form will be stored in a locked file that will be accessible only to authorized people involved with this project. We will carefully follow the coding, storage, and release plan explained in the *Description of the Research* section on pages 1 and 2 of this document.

Project Results

Your individual results from this research project will not be given back to you or put

into your medical records. If research from this project is published in professional journals, there will be no traditionally-used identifying information, such as your name, address, telephone number, or social security number, included in the publications. Some publications from this project will be found at the **[Project Name]** website.

Alternatives to Participating in the Project

The alternative option is not to participate in this project.

Voluntary Participation

The choice to participate in this research by donating your tissues and medical information is completely up to you. **No matter what you decide, your decision will not affect your medical care**.

Withdrawal from the Project

Once your coded samples have been distributed to the participating research laboratories and centers, and your information transferred to the appropriate databases, you will **not** be able to withdraw your information from this research project. However, you may be able to request the return or destruction of the tissue samples if you so desire.

Template

Contact Information

If you have any questions about the project or your participation, [*please use specific institutional language here, but do not automatically promise ability to withdraw*].

Agreeing to Participate in the Project

To participate in this research, you must agree to ALL of the following statements:

- I voluntarily agree to donate cancerous tissue and normal tissue to be used for this and for other research projects.
- I agree to release information from my medical records for this and for other research projects.
- I agree to have my coded genetic information and coded medical information placed into Internet-accessible databases as described in the *Storage and Release of Samples and Medical Information* section on page 2 of this document.
- I understand that my coded genetic information and coded medical information contained in the Internet-accessible databases will be used in this and in other research projects.
- I understand that there is a risk that someone in the future may be able to use information in these databases to identify me or possibly my relative(s).
- I agree to be contacted in the future about my willingness to provide additional samples or follow-up information about my health or medical care if it is required.

Please sign your name here if you agree to the six statements listed above.

Your signature: _____

Date: _____

Signature of Doctor/Nurse/Other Witness_____

Template

NOTE: Highlighted text of this document has to be used as provided in your Institution's informed consent forms for the samples to be acceptable to the project

OFFICE OF CANCER GENOMICS SUGGESTED LANGUAGE FOR RETROSPECTIVE TISSUE COLLECTIONS IN GENOMIC-SCALE PROJECTS

Purpose of the Project

We would like to invite you to participate in a research project called **[Project Name]**. The purpose of the **[Project Name]** project is to discover genetic changes associated with cancer. This should lead to better ways to prevent, detect, and treat cancer and, perhaps, other diseases as well.
This project is being sponsored by the National Cancer Institute (NCI), part of the government agency known as the National Institutes of Health (NIH).

Body tissues are made up of cells. Cells contain DNA, which is part of your unique genetic material that carries the instructions for your body's development and function. Cancer can result from changes in a person's genetic material, that cause cells to divide in an uncontrolled way and, sometimes, to travel to other organs. Currently, researchers and doctors know some of the genetic changes that can cause cancer, but they do not know all of the genetic changes that can cause cancer.

The **[Project Name]** project is designed to identify most of the genetic changes that can cause cancer in people. Therefore, we would like to study the genetic material from your cancer tissue as part of the **[Project Name]**. We will compare the genetic material from your cancer tissue to the genetic material from your normal tissue to find the differences that exist. By combining this information with information from your medical records, it may be possible to identify the genetic changes that are associated with your particular type of cancer. We will perform this same process with many (hundreds of) other people who have agreed to participate in this research project. By studying many different kinds of cancer in this way, we expect to identify most of the genetic changes associated with different kinds of cancer. Since we also will combine genetic information with information from medical records, such as the responses of different kinds cancers to different treatments, this project could lead to more knowledge about why certain cancers respond differently to treatments. With such knowledge, future treatments potentially could become customized to a patient's unique genetic make-up.

Description of the Research

Collection of Samples and Medical Information

- You already have had surgery as a part of the medical treatment that you agreed upon with your doctor. During your surgery, cancerous/tumor tissue was removed. As usually happens, when your cancerous tissue was removed, very small amounts of nearby normal tissue were removed along with it. Your surgery

Template

was not part of the **[Project Name]** research project. For this research project, we seek permission to receive some of these cancerous and normal tissues.

- If a second type of normal tissue (e.g., blood) was collected from you before or after your surgery, we request permission to obtain some of this tissue and genetic material that already may have already been extracted from this tissue.
- If an adequate blood sample is not available for this project, we will collect a sample from you by drawing approximately 4 tablespoons of blood from a vein in your arm. If you object to having blood drawn, we will collect normal tissue from you by swabbing cells from the inside of your cheeks.
- We will also collect information from your medical records, including your age, ethnic background, diagnosis, disease history, medical treatments, and response to treatments.

Coding of Tissue Samples and Medical Information

- Your tissues, blood or buccal (cheek swab) sample, and medical information will be labeled with a project-assigned ID.
- Only Dr. **[Physician Name]** at **[Institution Name]** will have the information that matches the code to traditionally-used identifying information, such as your name, address, phone number, or social security number. Dr. **[Physician Name]** will keep the information that matches the code to this traditionally-used identifying information in a safeguarded database. Only authorized people, who have specifically agreed to protect your identity, will have access to this database. All materials conveyed to the **[Project Name]** will be labeled with a project-assigned ID, removing traditionally-used identifying information, such as your name, address, phone number, or social security number. All other researchers and personnel, including those who will be working with your samples and medical information, will not have access to any of the traditionally-used identifying information about you.

Storage and Release of Samples and Medical Information

- Your coded tissue samples will be sent to an NCI-sponsored storage facility that will process the samples and then send portions of your samples to different types of laboratories as part of this project. One type of laboratory will analyze your DNA by a method called sequencing. Other laboratories will study your samples by different methods. The remaining portions of your samples will be stored for an unlimited period of time for future use in research related to cancer, or perhaps in other research projects.
- Information obtained from analyses performed on your coded samples and your coded medical information will be put into databases along with information from the other research participants. These databases will be accessible by the Internet.
    - Anonymous information from the analyses will be put into a completely public database, available to anyone on the Internet.
    - Your coded medical information and information from more detailed analyses of your coded samples will be put into a controlled-access database. The information in this database will be available only to researchers who have received approval from an NIH Data Access

Template

Committee. In gaining access to such information, researchers have to agree to use the data only for research projects and not to ever try to use it in order to identify the donor of the material. However, despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known

Please note that traditionally-used identifying information about you, such as your name, address, telephone number, or social security number, will NOT be put into either the public or controlled-access databases for this project.

Recontact

- In the future, we may want to obtain additional samples or follow-up information about your health or medical care. Should this be needed, a person from **[Institution Name]** will contact you to ask whether you would be interested in participating in this additional research.

Financial Compensation/Costs

You will not be paid to participate in this project. Your tissue samples and your medical information will be used only for research purposes and will not be sold. It is possible that some of the research conducted using your samples or information will eventually lead to the development of new diagnostic tests, new drugs or other commercial products. Should this occur, you will not receive any part of the profits generated from such products.

You will not incur any expenses from participating in this project. It is unlikely that you will be physically injured as a result of participating in this project. However, if you are physically injured as a result of participating in this project, emergency medical treatment for your research-related injury will be provided to you at no cost.

Potential Benefits of Participating in the Project

You should not expect to personally benefit from this research. The main reason you may want to participate is to help researchers and health professionals around the world to better understand the causes of cancer, and other diseases, and potentially to find better ways to prevent, detect, treat, and cure such illnesses. We hope that you will feel good knowing that you may be helping future cancer patients, as well as patients with other diseases.

Potential Risks of Participating in the Project

Physical Risks

- If noblood sample is taken from you, there are no physical risks associated with this project.
- There are very few physical risks if a blood sample is taken from you. Possible side effects from drawing the blood sample include mild pain, bleeding, bruising,

Template

and infection at the site of needle insertion. Fainting or light-headedness can sometimes occur, but usually last only a few minutes.

Psychological or Social Risks Associated with Loss of Privacy

- Your privacy is very important to us, and we use many safety measures to protect your privacy. However, despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.
- While neither the public nor the controlled-access databases developed for this project will contain information that is traditionally used to identify you (your name, address, telephone number, or social security number), technology may be developed in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a relative) in another database and be able to identify you (or your relative). It is also possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information back to you. Because some genetic variations can help to predict the current or future health problems of you and your relatives, this information may be of interest to employers, health providers, insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her relatives. Therefore, your genetic information could potentially be used in ways that could cause you or your family distress, such as by revealing that you (or a relative) carry a genetic disease or by leading to the denial of employment or insurance for you (or a relative).
- There also may be other privacy risks that we have not foreseen.

While we believe that the risks to you and your family are very low, we are unable to tell you exactly what all of the risks are. There are some state laws that protect against genetic discrimination by employers or insurance companies, but there is currently no federal law that prohibits such discrimination. We believe that the benefits of learning more about cancer and other diseases outweigh these potential risks.

Confidentiality

We will make every attempt to protect your confidentiality and to make sure that your personal identity remains anonymous. This signed consent form will be stored in a locked file that will be accessible only to a very small number of authorized personnel involved in this project. We will carefully follow the coding, storage, and release plan explained in the *Description of the Research* section on pages 1-3 of this document.

Project Results

Your individual results from this research project will not be given back to you or put into your medical records. If research from this project is published in professional journals, there will be no traditionally-used identifying information, such as your name, address, telephone number, or social security number, included in the publications. Some publications from this project will be found at the **[Project Name]** website.

Alternatives to Participating in the Project

The alternative option is not to participate in this project.

Voluntary Participation

The choice to participate in this research by donating your tissues and medical information is completely up to you. **No matter what you decide to do, your decision will not affect your medical care**.

Withdrawal from the Project

Once your coded samples have been distributed to the participating research laboratories and centers, and your information transferred to the appropriate databases, you will **not** be able to withdraw your information from this research project. However, you may be able to request the return or destruction of the tissue samples if you so desire.

Contact Information

If you have any questions about the project or your participation, [*please use specific institutional language here, but do not automatically promise ability to withdraw*].

Agreeing to Participate in the Project

To participate in this research, you must agree to ALL of the following statements:

- I voluntarily agree to donate cancerous tissue and normal tissue to be used for this and for other research projects.
- I agree to release information from my medical records for this and for other research projects.
- I agree to have my coded genetic information and coded medical information placed into databases accessible by the Internet, as described in the *Storage and Release of Samples and Medical Information* section on page 2 of this document.
- I understand that my coded genetic information and coded medical information in the Internet-accessible databases will be used in this and in other research

Template

projects.

- I understand that there is a risk that someone in the future might be able to use information in these databases to identify me or possibly my relative(s).
- I agree to be contacted in the future to see if I am willing to provide additional samples or follow-up information about my health or medical care if they are needed.

Please sign your name here if you agree to the six statements listed above.

Your signature: _____

Date: _____

Signature of Doctor/Nurse/Other Witness_____

Template

Office of Cancer Genomics
Material Transfer and Data Use Agreement Template

For Transfers to the Characterization Centers from Tissue Source Sites

This Material Transfer and Data Use Agreement (the "Agreement") is by and between _____ ("Provider"); and the **[Characterization Center name]**, ("**XXX**"), regarding the transfer of human specimens and associated data to the **XXX** as part of **[Project name]** project and associated research (the "Project"). Throughout this Agreement, Provider and **XXX** are collectively referred to as the "Parties" and individually as "Party." **XXX** is referred to as the "Recipient". This Agreement will become effective upon the date of the last signature affixed below (the "Effective Date").

WHEREAS, in order to improve the ability to diagnose, treat, and prevent cancer, the National Cancer Institute ("NCI"), member institute of the National Institutes of Health, an agency of the federal government, have jointly undertaken the Project as a comprehensive and coordinated research effort to accelerate the understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing;

WHEREAS, the major organizational components of the Project include multiple Cancer Genome Characterization Centers and Genome Sequencing Centers, which are third party institutions funded by the NCI (collectively the "Centers"), and a Data Coordination Center ("DCC"), which is operated by NCI through the NCI Center for Bioinformatics;

WHEREAS, the purpose of utilizing centralized centers is to minimize the variability introduced by the collection, processing and handling of selected human biospecimens and derivative materials that will be studied during the course of the Project;

WHEREAS, Recipients have been selected to act as characterization center(s), each pursuant to a subcontract with NCI's Operations and Technical Support ("OTS") contractor, SAIC-Frederick, Inc. (the "OTS Contractor"), and the tasks with which they are charged include receiving and processing human biospecimens, derivative materials and associated data and distributing all of the foregoing to the Centers and distributing only the associated data to the DCC;

WHEREAS, each Recipient, as a subcontractor of NCI's OTS Contractor, desires to receive and process biospecimens, derivative materials and associated data from the Provider and distribute the same to the Centers and the DCC, as appropriate;

WHEREAS, Provider desires to transfer certain human biospecimens, derivative materials, and associated data to Recipients (as determined by NCI's Statement of Work for the Project or as otherwise directed by NCI) for further distribution to the Centers and the DCC, as appropriate;

WHEREAS, each of the Centers and the DCC, pursuant to policies established as part of the Project, may not make a claim for intellectual property rights in the MATERIAL (as defined below), nor may they make a claim for intellectual property rights in DATA (as defined below) prior to its public availability;

Template

WHEREAS, Provider and Recipients desire to protect the privacy and provide for the security of certain information disclosed to Recipients in compliance with applicable laws and regulations; and

WHEREAS, Provider, if an entity of the United States of America ("U.S."), may be a covered entity subject to the Health Insurance Portability and Accountability Act of 1996, as amended ("HIPAA"), and, if not a U.S. entity, desires to protect the privacy of certain information disclosed to the Recipients in a manner consistent with HIPAA and the applicable laws of its jurisdiction that are similar in nature.

NOW, THEREFORE, in consideration of the mutual promises in this Agreement and for other good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties hereby agree as follows:

1. DEFINITIONS. Within this Agreement, the following terms will have the same meaning and effect as those used in the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 CFR Parts 160 and 164 ("HIPAA Privacy Rule"). These terms are repeated here for convenience.

(a) Under 45 CFR 160.103 ("Definitions"), a "covered entity" is an organization, individual, institution, or other entity that is subject to the standards, requirements, and implementation specifications of the HIPAA Privacy Rule with respect to protected health information.

(b) Under 45 CFR 164.514 ("Other requirements relating to uses and disclosures of protected health information"), "De-identified" information is information that formerly contained individually identifiable health information but which has had all unique identifying information, numbers, characteristics, and codes removed such that the information a record contains cannot be used alone or in combination with other information to identify the individual who is the subject of the information. Identifying information includes, but is not limited to, the 18 categories of identifiers described in 45 CFR 164.514(b)(2).

(c) Under 45 CFR 164.103 ("Definitions"), "Protected Health Information" or "PHI" means any information, whether oral or recorded in any form or medium: (i) that relates to the past, present, or future physical or mental condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual, and (ii) that identifies the individual or with respect to which there is a reasonable basis to believe the information can be used to identify the individual.

(d) Under 45 CFR 164.514(e)(2) ("Implementation Specification: Limited data set"), a "limited data set" (herein "LDS") is protected health information that excludes the 16 direct identifiers listed in that section. Any such information that identifies the individual who is the subject of the PHI, his or her relatives, employers, or household members must be removed for the PHI to constitute an LDS. Unlike de-identified PHI, an LDS *may* contain postal address information, in the form of a town, city, State, or zip code only; age; specific dates, for example, dates of birth, death, admission, treatment, or release; and any other information, not specifically listed in that section, that could be used alone or in combination with other information to identify a specific individual.

2. DESCRIPTION OF MATERIAL AND DATA.

Template

(a) The material to be transferred ("ORIGINAL MATERIAL") is a set of human biospecimens described specifically as: Human Tumors, Matching Normal Specimens or Blood.

(b) The data to be transferred to each Recipient are clinical, biological, technical and/or other information describing the ORIGINAL MATERIAL ("DATA"). Some of the DATA may be Protected Health Information and will be transferred in the form of an LDS.

3. COLLECTION OF MATERIAL AND DATA. The Provider represents and warrants to Recipients that: (a) all ORIGINAL MATERIAL and DATA provided to Recipients by Provider were collected pursuant to and in accordance with a protocol approved by an Institutional Review Board ("IRB"); (b) the IRB's oversight of the collection of any ORIGINAL MATERIAL and DATA included a review of all necessary informed consents and authorizations, which consents do not prohibit redistribution of the ORIGINAL MATERIAL or materials derived from the ORIGINAL MATERIAL, e.g., DNA and RNA products ("DERIVATIVE MATERIAL," together with the ORIGINAL MATERIAL, the "MATERIAL") or DATA in the manner described in Section 4 of this Agreement; (c) the transfer, processing and analysis of the ORIGINAL MATERIAL and DATA, as part of the Project and for the Purpose, is authorized by or consistent with the general principles of the informed consent of the patient supplying such ORIGINAL MATERIAL and DATA, as determined by an IRB; and (d) the collection of the ORIGINAL MATERIAL and DATA was conducted in compliance with all applicable laws, regulations and policies for the protection of human subjects, including, in the case where Provider is a covered entity, 45 CFR Part 46, "Protection of Human Subjects" (the "Common Rule") and the HIPAA Privacy Rule, and any necessary approvals, authorizations, human subjects assurances, informed consent documents, and IRB approvals were obtained.

4. TRANSFER OF ORIGINAL MATERIAL AND DATA; PURPOSE. (a) Provider agrees to provide to each Recipient the ORIGINAL MATERIAL and DATA, in the form of an LDS pursuant to Case Report Forms provided by the Recipient to the Provider, in accordance with applicable laws, regulations and policies, including but not limited to the Common Rule, the HIPAA Privacy Rule, and any necessary authorizations, human subjects assurances, informed consent documents, and IRB approvals. The ORIGINAL MATERIAL and DATA to be transferred to each Recipient will be determined in accordance with NCI's Statement of Work for the Project or as otherwise directed by NCI. The sole and limited purpose of the Provider's transfer to Recipients of the DATA is to enable each Recipient to receive, process and distribute the MATERIAL and the DATA, in the appropriate form as indicated below, to the other Recipient, the Centers and the DCC at NCI in fulfillment of each Recipient's contractual obligations to NCI's OTS Contractor (the "Purpose"). If Provider is a HIPAA Covered Entity, the Parties expressly intend for this Agreement to constitute a data use agreement, authorizing use and disclosure only in furtherance of the Purpose, in accordance with 45 CFR 164.514(e)(4). Provider is responsible for removing all of the prohibited direct identifiers from the DATA, such that the DATA will be in the form of an LDS, before transfer to Recipients.

(b) Provider has the authority and hereby grants each Recipient explicit permission to further distribute the MATERIAL and De-identified DATA to the Centers.

(c) Provider has the authority and hereby grants each Recipient explicit permission to further distribute the MATERIAL and DATA, in the form of an LDS, to the other Recipient upon execution by Research Institute and Recipient of a data use agreement that is consistent with the requirements of the HIPAA Privacy Rule.

Template

(d) Provider has the authority and hereby also grants each Recipient explicit permission to further distribute the DATA, in the form of an LDS, to the DCC upon execution by each Recipient and NCI of a data use agreement that is consistent with the requirements of the HIPAA Privacy Rule. Furthermore, Provider acknowledges and agrees that each Recipient may allow the DCC to provide all or part of the LDS to third parties pursuant to separate data use agreements that are no less restrictive than this Agreement and that prohibit such third parties from further distributing the LDS.

(e) The Agreement does not restrict the Provider's right to distribute the MATERIAL and DATA to third parties.

5. RESPONSIBILITIES AND AUTHORIZATIONS OF RECIPIENT

(a) Each Recipient's IRB or equivalent has approved each Recipient's participation in the Project. Each Recipient agrees to handle and distribute the MATERIAL in accordance with all applicable laws, regulations and policies, including, as applicable, the Common Rule, the HIPAA Privacy Rule, and any necessary human subject's assurances, informed consents and IRB approvals.

(b) Each Recipient further agrees that it will only use and/or disclose the DATA for the Purpose described herein and shall not use or disclose the DATA in a manner inconsistent with the HIPAA Privacy Rule.

(c) Each Recipient is not authorized and shall not further disclose the DATA other than as permitted by this Agreement or as otherwise required by law. Neither Recipient shall distribute the DATA to other third parties without written consent from Provider and NCI's OTS Contractor.

(d) Each Recipient shall use appropriate administrative, technical, and physical safeguards to prevent use or disclosure of the DATA other than as provided for in this Agreement.

(e) Each Recipient shall notify Provider in writing within five (5) working days of its discovery of any use or disclosure of the DATA not permitted by this Agreement of which the respective Recipient, its officers, employees, or agents become aware. Each Recipient shall take (i) prompt corrective action to cure any deficiencies or (ii) any action pertaining to such unauthorized disclosure required by applicable federal law.

(f) Each Recipient shall ensure that any of its agents or subcontractors agree with Recipient in writing that such agent or subcontractor will hold any DATA transmitted from the respective Recipient to such agent or subcontractor confidential and will use or disclose the information only for the purpose for which it was used or disclosed to the agent or subcontractor, or as required by law. Additionally, the agent or subcontractor shall notify the applicable Recipient of any instances, of which it is aware, in which the DATA has been used or disclosed inconsistent with this Agreement.

(g) Each Recipient agrees to not identify or contact any donor, or living relative of a donor, who provided the MATERIAL or any DATA received by Recipient under this Agreement from Provider. Furthermore, each Recipient will not attempt to obtain or otherwise acquire any PHI associated with the MATERIAL beyond that which is provided in the DATA by the Provider.

(h) Each Recipient will retain and abide by this Agreement for as long as it retains the DATA or other PHI received from the Provider, plus 6 (six) years after the date it returns or destroys all such information.

Template

6. BREACH OR VIOLATION. Provider is not responsible for either Recipient's violations of this Agreement, unless Provider knows of a pattern of activity or practice that constitutes a material breach or violation of this Agreement, in which case it must take reasonable steps to cure the breach, end the violation or withhold the LDS or other PHI delivered to Recipient. If this is not possible, the breach will be reported to the Secretary of the Department of Health and Human Services ("DHHS"). Notwithstanding anything to the contrary, each Recipient is not responsible for the other Recipient's violations of this Agreement.

7. THE MATERIAL AND DATA ARE NOT FOR USE IN HUMAN SUBJECTS OR FOR THE TREATMENT OR DIAGNOSIS OF HUMAN SUBJECTS.

8. DISCLAIMER. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature and may have hazardous properties. SUBJECT TO THE REPRESENTATIONS IN SECTION 3 ABOVE WITH RESPECT TO THE MATERIAL OR DATA, PROVIDER MAKES NO REPRESENTATIONS AND EXTENDS NO WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THERE ARE NO EXPRESS OR IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, OR THAT THE USE OF THE MATERIAL OR DATA WILL NOT INFRINGE ANY PATENT, COPYRIGHT, TRADEMARK, OR OTHER PROPRIETARY RIGHTS.

9. DISPOSAL OF MATERIAL AND DATA. At the end of its subcontract with the NCI's OTS Contractor or upon the termination of this Agreement by any Party, each Recipient will dispose of the ORIGINAL MATERIAL and DATA in its possession in the manner decided at the sole discretion of NCI OTS Contractor and consistent with law and the informed consent of the individual providing the ORIGINAL MATERIAL. Such disposition may include, but is not limited to, continued storage on behalf of Provider for future research, transfer to the Provider, use in an expansion of the Project, transfer to another organization acting on NCI's behalf, or destruction. NCI shall be responsible for ensuring that any directive given to either Recipient regarding the disposition of the ORIGINAL MATERIAL and DATA is consistent with the informed consent of the patient who provided such ORIGINAL MATERIAL. Provider acknowledges that any ORIGINAL MATERIAL transferred by either Recipient to the Centers and/or the DCC may be destroyed as a consequence of the analyses conducted in accordance with the Project.

10. INTELLECTUAL PROPERTY. Provider explicitly retains ownership of ORIGINAL MATERIAL and DATA. Provider acknowledges and agrees that it does not by virtue of this Agreement acquire any intellectual property rights in the future inventions or discoveries made by third parties using the MATERIAL or DATA distributed by Recipient. Each Recipient acknowledges that it serves only as the custodian of the MATERIAL and DATA, and therefore agrees that it does not by virtue of this Agreement acquire any intellectual property rights in the MATERIAL, nor any future intellectual property rights in any research conducted by third-parties using the MATERIAL or DATA.

11. RELATIONSHIP OF THE PARTIES. Each Party to this Agreement is an independently contracting party. Nothing in this Agreement shall constitute, be construed, or create an employment relationship, a partnership, or a joint venture among any of the Parties. Notwithstanding anything to the contrary, each Recipient will be responsible for its own acts and

Template

omissions under this Agreement and the results thereof. Neither Recipient will be responsible for fulfilling the covenants, obligations, or promises of the other Recipient under this Agreement.

12. ASSIGNMENT; SUCCESSORS AND ASSIGNS; NO THIRD-PARTY RIGHTS. Neither Recipient may assign its rights or cause to be assumed its obligations hereunder without the prior written consent of Provider, which consent shall not be unreasonably withheld or delayed. Subject to the foregoing, this Agreement shall apply to, be binding in all respects upon and inure to the benefit of the Parties hereto and their respective successors and assigns. Nothing expressed or referred to in this Agreement shall be construed to give any person or entity other than the Parties hereto any legal or equitable right, remedy or claim under or with respect to this Agreement or any provision of this Agreement.

13. COST. The MATERIAL and DATA are provided at no cost to Recipients.

14. SHIPPING. Provider will notify each Recipient, as applicable, when the MATERIAL and DATA are ready for shipment. Each Recipient will be responsible for the pick-up and shipment, including shipping costs, of the MATERIAL and DATA sent to it.

15. ENTIRE AGREEMENT. This Agreement constitutes the entire agreement between the Parties with respect to the subject matter hereof, and supersedes and replaces all prior agreements, understandings, commitments, communications and representations made between the Parties, whether written or oral, with respect to the subject matter hereof. This Agreement may not be amended, supplemented, or otherwise modified except by a written agreement executed by each of the Parties. Any Party has the right to terminate this Agreement at any time upon sixty (60) days prior written notice to the other Parties.

16. EXECUTION OF AGREEMENT. This Agreement may be executed in two or more counterparts, each of which will be deemed to be an original copy and all of which, when taken together, will be deemed to constitute one and the same agreement. The exchange of copies of the Agreement and of signature pages by facsimile transmission will constitute effective execution and delivery of this Agreement as to the Parties hereto and may be used in lieu of the original Agreement for all purposes. Signatures of the Parties transmitted by facsimile will be deemed to be their original signatures for all purposes.

SIGNATURES ON FOLLOWING PAGES

Template

Signature for Provider

Provider Scientist:
Provider Organization:
Address:

Name of Authorized Official:
Title of Authorized Official:

_____
Signature of Authorized Official Date

Certification of Provider Authorized Official: This Agreement __has / __has not been modified. If modified, the modifications are attached.

Template

[This Institutional Certification should be submitted on the PI's institutional letterhead.]

Date: November XX, 2009

[Insert name and address of Program Director or other person at your institute who will be responsible for registering the dataset with dbGap]

Re: Certification of [name of PI's institution] to Accompany Submission of the Dataset for the HMP Demonstration Project, [insert name of Project] to the NIH Database of Genotypes and Phenotypes (dbGaP).

Dear Dr. _____:

[Name of PI's institution] adheres to the *Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS),* Notice Number: NOT-OD-07-088. [Name of PI's institution] provides the following Certification in regard to the Dataset for the [name of Project], which is being deposited into dbGaP.

- The data submission is consistent with all applicable laws and regulations, as well as institutional policies.

- All uses of these data that are deemed acceptable and approved per NIH policy and that follow the dbGaP procedures for access are allowable, with the following restriction:

  Data Use Limitation
  These data may be be used for …..

- The identities of research participants will not be disclosed to dbGaP

- An Institutional Review Board has reviewed and verified that:

  - The submission of data to dbGaP and subsequent sharing for research purposes are consistent with the informed consent of the study participants from whom the data were obtained;
  - The plan for de-identifying datasets is consistent with the standards outlined above;
  - [Name of institution] has considered the risks to the individuals, their families, and groups or populations associated with data submitted to dbGaP and determined risks to be reasonable in relation to anticipated benefits to society; and
  - The phenotype data to be submitted were collected in a manner consistent with 45 CFR Part 46. .

The suggested Acknowledgement Statement to accompany the data set is:

Template

Acknowledgement Statement

[Insert desired language for Acknowledgement Statement here.]

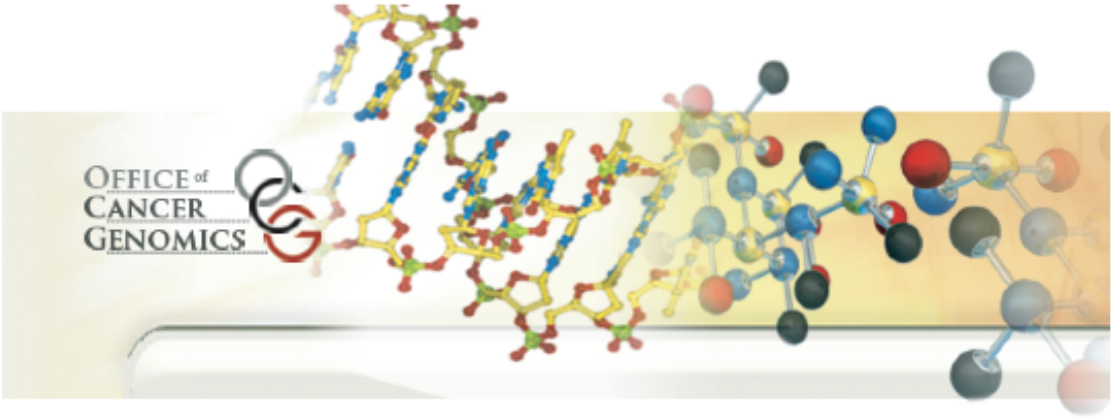
If additional information is required, please do not hesitate to contact us.

Sincerely,

[Need signatures from both the signing official at the PI's institution and the PI for the Project.]

Template

National Cancer Institute



HTMCP GENERAL PROTOCOLS

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

Adopted:_____4/26/2010__
2nd Version :_____09/01/2010__
3rd Version :_____
Reviewed:_____
4th Version :_____

DOCUMENT REQUIREMENTS FOR SAMPLE SUBMISSION TO THE HIV+ TUMOR MOLECULAR CHARACTERIZATION PROJECT

I. INTRODUCTION:

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Office of HIV and AIDS Malignancy (OHAM) have developed an initiative to compare the cancer related alterations in HIV+ patients and HIV- patients. It is possible that the comparison of transcriptomes and genomes between tumors from HIV^+ and HIV^- individuals may or may not identify novel non-human sequences which could suggest the presence of transcripts from known or hitherto undiscovered oncogenic viral agents.

It is imperative that all personnel involved in the project read all the protocols and adhere to them at all times. It is your responsibility as a contributor to the HTMCP to familiarize yourself with all aspects of the procedures and assure their compliance.

A. SCOPE AND PURPOSE:

1. To list all the documents needed in order to start collection of samples for the HIV+ Tumor Molecular Characterization Project (HTMCP).
2. This protocol applies to all Tissue Source Sites (TSSs) providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times and which samples were affected. This information should be given within 48 hours of the occurrence to the project team by sending an e-mail to Dr. Jean C. Zenklusen (**jz44m@nih.gov)** with the details.

B. REQUIREMENTS:

1. Every TSS must have an IRB approved protocol in place that allows collection of tumor tissue, matched normal tissue (blood, whenever possible) and clinical data that can be used in a characterization project. The protocol must have explicit language

permitting the molecular characterization of the samples by genomic-scale methodologies, and subsequent deposition of the data into a public, but protected database.

2. Every patient accrued to the project must be enrolled in the protocol and agree to participate by signing an informed consent.
3. If you require assistance drafting such protocol or informed consent form, please contact the Project Team representative (PT, see address in contact sheet). OCG has templates that contain the appropriate language.
4. TSSs must have in place a materials transfer agreement (MTA) with both the Genome Science Center at British Columbia (GSC-BC, see address in contact sheet) and the Pathology Coordinator (see address in contact sheet) to allow transfer of tissues and pathology reports. A sample MTA can be provided by PT upon request.
5. OCG will store a copy of the IRB-approved protocol and a blank informed consent form. Additionally, certification that such protocol exists, and that patients have been consented, must be produced by the TSS Institution before the samples can be accepted and costs can be reimbursed. A template of such certification document can be found in Appendix A.
6. The completed Institutional certification must be sent to PT before any sample can be shipped.

Adopted:_____4/26/2010__
2nd Version :_____9/01/2010__
3rd Version :_____
Reviewed:_____
4th Version :_____

PROCESSING TISSUE FOR MOLECULAR CHARACTERIZATION OF HIV+ TUMORS

I. INTRODUCTION

A. SCOPE AND PURPOSE:

1. To establish a procedure for tissue processing and storage by Tissue Source Sites (TSS).
2. This protocol applies to all TSSs providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times and which samples sere affected. This information should be given within 48 hours of ocurrence to the project team by sending an e-mail to Dr. Jean C. Zenklusen (**jz44m@nih.gov)** with the details.

B. SAFETY PRECAUTIONS:

1. Wear personal protective equipment (PPE) such as lab coats and gloves.
2. Liquid nitrogen is extremely cold and can cause 'burns'. Wear gloves that are specially made to withstand liquid nitrogen, eye protection (preferably Face Shield) and a lab coat to protect skin from splashes and spills. Liquid nitrogen is an asphyxiant; be sure to use in a well-ventilated area.
3. Acute overexposure to formaldehyde solutions and/or vapors causes severe eye, skin, and respiratory tract irritation.

C. EQUIPMENT AND MATERIALS:

1. Personal protective equipment (PPE) to include heavy duty gloves, eye protection (preferably Face Shield), lab coat and closed-toe shoes
2. Plastic cassette mold(s) for Formalin fixation.
3. Cryovials (2mL vials, e.g. ChartBiomed, Part Number 10778828)
4. Freezer resistant labels with project-assigned ID (obtained from Project Team, see HTMCP SOP #101)
5. Dewar thermo-flask
6. Isopentane
7. Liquid Nitrogen
8. Formalin (10% solution)

9. Fine point Cryomarker (e.g., Nalge Nunc Cryomarker Black #6313-0020)

MARK ALL CONTAINERS WITH THE LABELS CARRYING PATIENT PROJECT-ASSIGNED ID OBTAINED PRIOR TO SURGERY.

II. PROCEDURE:

A. A lymph node or tissue diagnosed as Diffuse Large B-Cell Lymphoma should be processed as follows:

1. Wearing sterile gloves, cut the lymph node into multiple 2 mm thin sections using a sterile scalpel.
2. Place tissue into various containers as follows:
   i. **24-HOUR FORMALIN FIXATION**: Submit two or three 2 mm representative tissue pieces for diagnosis, including lymph node capsule (1-2 blocks) to your Histology Lab. Tissue in formalin should be no more than 2 mm in thickness for proper fixation.
   ii. **FREEZING TISSUE**: Select two or three representative pieces of tissue measuring about 10 x 10 x 2 mm in dimension. Freeze as many pieces as possible. Do not freeze the tissue with Freon.
   Freeze the tissues as described below:

(i) Perform snap freezing of fresh tissue ASAP

1. It is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is ablated from patient.
2. Do not perform snap freezing with bare hands. Wear gloves at all times.

(ii) Set Up Freezing Station

1. Fill a small 100 ml metal beaker about 1/4 full with isopentane (2-methylbutane, certified grade).
2. Fill the Dewar thermo-flask about 1/3 full with liquid nitrogen.
3. Use extreme caution when dispensing liquid nitrogen

(iii)Label Cryovial As Needed

1. Use a cryomarker for labelling.
   a. Use a cryovial for tissue snap freezing.
   b. Label cryovial with freezer-resistant labels obtained prior to surgery (see H+ TMCP SOP #101).

(iv)Freezing Tissue in Cryovial

a. Cut a 1cm by 3 cm strip of histowrap

b. Put the tissue on the histowrap strip

c. Place the histowrap strip containing tissue into a labelled cryovial, using a pair of forceps.

d. Screw on the cap **tightly** or else isopentane will seep into the vial during freezing and create a liquid in the vial upon thawing.

e. Lower the 100 ml metal beaker containing isopentane half-way

into the liquid nitrogen for cooling. The liquid nitrogen will boil as the beaker is lowered, when the isopentane is reaching its freezing point the tone of the boiling will increase for 2-3 seconds.

f. Lift the beaker out of the liquid nitrogen once you see beads of solid isopentane at the bottom of the beaker (about 2 minutes).

g. Use long forceps to hold the cryovial down into the cooled isopentane. Hold for at least 1 minute.

h. Use the long forceps to take out the cryovial/ frozen tissue.

i. Store Frozen tissue vial(s) in Liquid Nitrogen Storage Tanks.

B. Make a gross report of the sample using the dictation template below.

C. Any questions regarding this protocol should be directed to the appropriate Pathology Coordinators listed in the Contact List.

THE FROZEN SPECIMENS SHOULD BE KEPT FROZEN ON DRY ICE AT ALL TIMES DURING TRANSPORT TO AND FROM STORAGE TANKS.

H+ TMCP STUDY GROSS DICTATION TEMPLATE

History:

The patient is a…

Source/Gross:

The specimen is received (**fresh vs. fixed**) in (**# containers**), each labeled with the project-assigned ID "#" and designated "#." The specimen consists of (**gross to include number of fragments, size, appearance, etc.**)

Specimens submitted are:

Fixed in formalin for 24 hours – (**size, # of pieces in each block, and cassette designation**)

Snap Frozen – (**size and # of blocks**)

Adopted:_____4/26/2010__
2nd Version :_____9/01/2010__
3rd Version :_____
Reviewed:_____
4th Version :_____

PROCESSING NON-TUMOR SAMPLES FOR THE HIV+ TUMOR MOLECULAR CHARACTERIZATION PROJECT: BLOOD AND BUCCAL CELLS

I. INTRODUCTION:

A. SCOPE AND PURPOSE:

1. To establish a common procedure for processing non-tumor samples (either blood or buccal swabs) previous to shipment to the Genome Science Center at British Columbia (GSC-BC) by tissue source sites (TSS).
2. This protocol applies to all TSSs providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times and which samples were affected. This information should be given within 48 hours of occurrence to the project team by sending an e-mail to Dr. Jean C. Zenklusen (**jz44m@nih.gov)** with the details.

B. SAFETY PRECAUTIONS:

1. Wear personal protective equipment (PPE) such as lab coats and gloves.

C. EQUIPMENT AND MATERIALS:

1. Personal protective equipment (PPE) to include heavy duty gloves, eye protection (preferably Face Shield), lab coat and closed-toe shoes
2. Clinical Centrifuge
3. Vortex
4. Cryovials (2mL vials, e.g., ChartBiomed, Part Number 10778828)
5. Cotton tipped swabs (e.g., Catch-All swabs, catalog # QEC091H; Epicentre Biotechnologies, Madison, WI, USA) OR Dacron swabs (e.g, MasterAmp™ Buccal Swab Brushes, catalog # MB100BR; Epicentre Biotechnologies, Madison, WI, USA)
6. Freezer resistant labels with project-assigned ID (obtained from Project Team, see HIV+TMCP SOP #101)
7. TE buffer (10 mM Tris·Cl; 1 mM EDTA, pH 8.0)
8. Dewar thermo-flask
9. Liquid nitrogen
10. Isopentane (2 methyl butane)

MARK ALL CONTAINERS WITH THE LABELS CARRYING PATIENT PROJECT-ASSIGNED ID OBTAINED PRIOR TO SURGERY.

II. PROCEDURE:

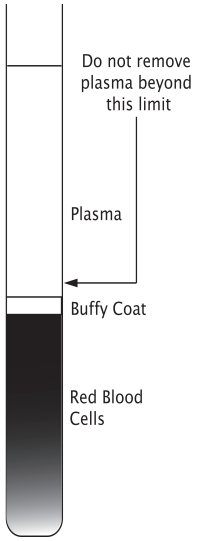
A. BLOOD SAMPLES:

a. Collect 10 ml of blood according to standard procedures in tubes containing anticoagulant (recommended anticoagulant is sodium citrate or heparin).

b. **Blood Separation**:

1. Fractionate the whole blood by centrifuging at 1500-2000 *X* g for 10-15 min at room temperature. This will separate the blood into an upper plasma layer, a lower red blood cell (RBC) layer, and a thin interface containing the white blood cells (WBCs) / buffy coat (see Figure 1). Fractionate the blood as soon as possible after collection.

NOTE: In a typical clinical centrifuge 1500-2000 *X* g is ~3000-3400 rpm. Check the appropriate settings for your centrifuge using the nomogram in your user's manual.



2. Use a disposable, plastic transfer pipet (e.g. Falcon Cat #357524) to aspirate off the plasma (upper layer) down to ~1 mm from the buffy coat (see Figure). Discard the plasma. When removing the plasma do not disturb the WBC layer, also called the buffy coat, which forms a thin film between the upper plasma layer and the lower layer of packed RBCs. Samples with exceptionally high WBC counts will have a thicker buffy coat.
3. Recover the WBCs in ≤0.5 ml by aspiration with a fresh disposable pipette or a Pasteur capillary pipette.
4. Dispense the recovered buffy coat onto a cryovial labeled with a freezer-resistant label obtained prior to surgery from the Project Team (HIV+TMCP SOP #101). Screw on the cap **tightly** or else isopentane will seep into the vial during freezing and create a liquid in the vial upon thawing.

c. Set Up Freezing Station

1. Fill a small 100 ml metal beaker about 1/4 full with isopentane (2-methylbutane, certified grade).
2. Fill the Dewar thermo-flask about 1/3 full with liquid nitrogen.
3. Use extreme caution when dispensing liquid nitrogen

d. Freezing Blood Cells in Cryovial

1. Lower the 100 ml metal beaker containing isopentane half-way into the liquid nitrogen for cooling. The liquid nitrogen will boil as the beaker is lowered, when

the isopentane is reaching its freezing point the tone of the boiling will increase for 2-3 seconds.

2. Lift the beaker out of the liquid nitrogen once more than you see beads of solid isopentane at the bottom of the beaker (about 2 minutes).
3. Use long forceps to hold the cryovial down into the cooled isopentane. Keep submerged for at least 1 minute.
4. Use the long forceps to take out the cryovial/ frozen tissue.
5. Store frozen tissue vial(s) in liquid Nitrogen storage tanks or -80ºC freezers.

B. BUCCAL SWABS:

1. To ensure adequate DNA collection, we recommend that the participant rub the inside of both cheeks firmly for a minimum of 1 minute with a minimum of three swabs.
2. Once swabbing is complete, the tips of each swab should be cut with a pair of scissors and placed into 1.5 ml microcentrifuge tube (one per tip). Add 1 ml TE buffer, close lid and vortex for 10s.
3. Remove the swab from the microcentrifuge tube using forceps. Squeeze as much liquid as possible out of the swab by pushing the swab against the side of the microcentrifuge tube. Combine all liquid from all tubes into a single microcentrifuge tube.
4. Centrifuge the microcentrifuge tube containing buccal cells at maximum speed for 10 s. Discard the supernatant and wash the buccal cells by resuspending the pellet in 1 ml TE and vortexing for 1 min.
5. Centrifuge the microcentrifuge tube containing buccal cells at maximum speed for 10 s. Discard the supernatant and resuspend the buccal cell pellet in 30 µl TE. Place suspension into a screw cap cryovial. Cell suspensions should then be frozen as described above.

Any questions regarding this protocol should be directed to the appropriate Pathology Coordinators listed in the contact list.

THE FROZEN SPECIMENS SHOULD BE KEPT FROZEN ON DRY ICE AT ALL TIMES DURING TRANSPORT TO AND FROM STORAGE TANKS.

Adopted:_____4/26/2010__
2nd Version :_____9/01/2010__
3rd Version :_____1/06/2011__
Reviewed:_____
4th Version :_____

SHIPPING CRYOPORTS CONTAINING FROZEN BIOSAMPLES FOR PROCESSING AND EXTRACTION OF NUCLEIC ACIDS

I. INTRODUCTION:

Cryoports are shipped from the Genome Sciences Center at the British Columbia Cancer Agency (GSC-BC) to the Tissue Source Site (TSS). TSSs are instructed to use this SOP when shipping samples to the GSC-BC.

A. SCOPE AND PURPOSE:

1. To establish a procedure for personnel in shipping the cryoports.
2. This procedure applies to all laboratory personnel.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times and samples affected. This information should be given immediately to the project team by sending an e-mail to Dr. Jean C. Zenklusen (**jz44m@nih.gov)** with the details.

B. SAFETY PRECAUTIONS:

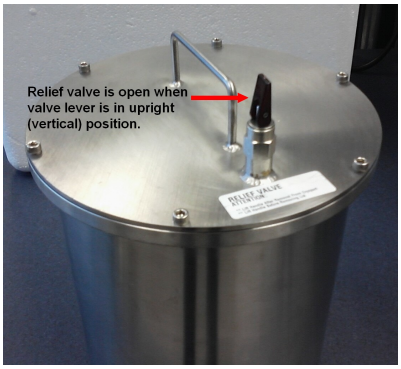
1. Wear personal protective equipment (PPE) such as lab coats and gloves.
2. Liquid nitrogen is extremely cold and can cause 'burns'. Wear gloves that are specially made to withstand liquid nitrogen, eye protection and a lab coat to protect skin from splashes and spills. Liquid nitrogen is an asphyxiant; be sure to use in a well-ventilated area.
3. Always keep the cryoport in the upright position.

C. EQUIPMENT AND MATERIALS:

1. Cryoport, obtained in 3 or 4 days in advance from the GSC-BC Coordinator (see below).
2. Personal protective equipment (PPE) to include heavy duty gloves, eye protection (preferably Face Shield), lab coat and closed-toe shoes
3. Shipping documents

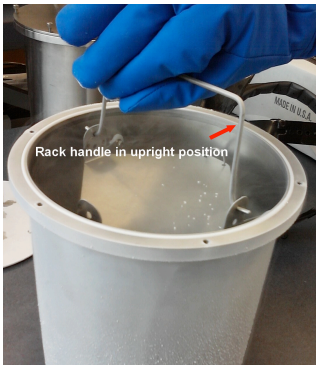
II. PROCEDURE:

1. Request cryoport from GSC-BC shipping coordinator 3-4 days in advance of sectioning samples.
2. Complete the appropriate shipping forms needed for the sample(s).
3. Complete the sample shipping document with the project-assigned ID obtained prior to surgery, the sample type information and any comments. Sign and date the form and have a second individual verify the contents of the shipment and sign and date the form.
4. Don personal protection equipment.
5. To unlock the cryoport shipping carton, cut the zip ties securing the two twist latches on the outer lid, flip the butterfly handles outwards and turn counterclockwise to disengage the latches. Carefully open the cryoport shipping carton lid. The cryoport cork with attached data logger will be visible. It is not necessary to remove the cryoport from the shipping carton.
6. Extract the Allen key from the small pouch attached to the underside of the shipping carton lid. Leave the pouch attached to the lid.
7. Remove the large ziplock bag attached to the underside of the shipping carton lid. The bag contains the Cryoport Temperature Log sheet, an IATA shipping label, a FedEx Airbill Tie-On tag, a leak-proof biohazard bag, absorbent cloth sheets, and zip-ties.
8. Fill out the information on the "TSS Inbound" section of the Cryoport Temperature Log.
   (1) The internal temperature of the cryoport is displayed on the data logger.
   (2) If the cryoport will not be returned within 24 hours, please record the temperature each subsequent day after arrival in the "Temperature Records" section of the Cryoport Temperature Log.
   (3) If the temperature is -180°C or colder, it can be used to ship the samples to the GSC-BC. ALERT: If the temperature is warmer than -180°C, please contact the GSC-BC coordinator for instructions before proceeding further.
9. Remove the zip tie securing the cryoport cork lid to the cryoport. Lift the cork up to gain internal access to the cryoport. The top of the inner, sealed, stainless steel canister will be visible. NOTE: Only remove the canister when you are ready to place your samples inside.
10. Carefully remove the stainless steel canister by grabbing the handle at the top and slowly lifting the canister up and out of the cryoport. ATTENTION: After removing the stainless steel canister from the cryoport, immediately lift the black lever of the relief valve on the top of the canister up into a vertical position to release any pressure/vacuum inside the canister.

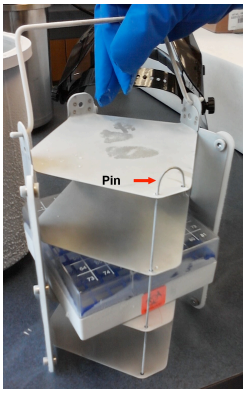


11. Place the cork back in the cryoport while you perform the following steps. ATTENTION: Be careful that the temperature probe extending from the bottom of the cork goes into the cryoport and does not get trapped between the cork and the side of the cryoport.

    (a) Use the Allen key to remove the 6 Allen bolts securing the lid to the stainless steel canister. Be careful not to misplace any of the bolts. Ensure that the relief valve lever is still in the upright position, and lift the lid off the container. The top of the stainless steel rack will be visible.



    (b) The rack has a hinged metal handle on top. Swing the handle upright (see photo at right) and then pull the rack up to lift it out of the canister.



    (c) To access the freezer box, slide the containment pin at the front of the rack (see photo at right) up and out of the guide holes, then slide the freezer box out of the rack.

    (d) Place the cryovials containing your samples into the cryovial box, then seal the cryovial box inside the supplied biohazard ziplock bag along with 1 or more sheets (folded in half) of the absorbent cloth, as required. Each sheet is capable of absorbing 250mL of liquid. Ensure most of the air is pressed out of the bag before sealing. Fold the excess length of the biohazard bag under one edge of the freezer box (see photo at left).

(e) Place the cryovial box back into a shelf on the rack, orienting the folded edge of the plastic bag to one side of the rack (see photo at right). Replace the containment pin by sliding it down through the top of the rack and the guide holes on each shelf. Ensure the top of the pin goes through the locking guide hole on the top of the rack (see photo at right).

(f) Use the handles on top of the rack to carefully lower the apparatus back into the stainless steel canister. The fit is quite snug; you may need to slightly adjust the box position as you lower the rack into the canister in order for the box and bag to clear the edges of the canister.

(g) Ensure that the top flange of the stainless steel canister and the underside of the canister lid are dry. Place the lid on the canister and align the holes in the lid with the screw holes in the canister. Ensure the relief valve lever is in the upright position, and use the Allen key to secure the lid with the 6 Allen bolts. Once all the bolts are secured, close the relief valve by flipping the lever downward into the horizontal position.

12. Carefully lower the stainless steel canister back into the cryoport, and replace the cork. ATTENTION: Be careful that the temperature probe extending from the bottom of the cork goes into the cryoport and does not get trapped between the cork and the side of the cryoport.
13. Align the openings in the side of the cork lid with the openings in the cryoport neck, and secure with one of the supplied zip ties. Cut most of the excess length off of the zip tie.
14. Allow the cryoport temperature to stabilize. When the datalogger displays a stable temperature reading, record the temperature in the "TSS Outbound" section of the Cryoport Temperature Log.
15. Place the Allen key back into the designated bag attached to the underside of the shipping carton lid. Ensure the enclosure is properly sealed so the Allen Key does not fall out during transport.
16. Carefully close the shipping carton lid. Engage both of the twist latches by interlocking the catches, turning the butterfly handles clockwise to close down the latch, and then folding handles down so they are flush with the body of the latch. Secure each latch with two zipties as illustrated by the image on the shipping carton.

17. Place the provided label with the IATA mark (UN 3373, Biological Substance, Category B) in the clear plastic envelope that is attached to the side of the shipping carton, such that the label is clearly visible and in the upright orientation. Ensure the plastic envelope is sealed.
18. Place all shipping documents, including the Sample Shipping Document, the Cryoport Temperature Log, and 5 copies of the Commercial Invoice, into the Airbill pouch on the Airbill Tie-On tag. Seal the pouch. Attach the Tie-On tag to the handle closest to the IATA mark on the shipping carton, and secure with a zip tie.
19. Notify the shipping carrier for pick-up. Under normal conditions, shipments should only be sent to GSC-BC on Monday through Wednesday. If an exception is needed, the GSC-BC must be contacted at 604-877-6088 for further instructions and to alert the GSC-BC personnel of any schedule changes.
20. TSS personnel will notify the coordinator by email stating the cryoport is being returned with tissue samples back to the GSC-BC, and providing the tracking number. Also provide an electronic copy of the Sample Shipping Document.
21. The GSC-BC Coordinator will track the cryoport in transit.
22. If there are any exceptions to the normal shipping schedule or in the event of an anticipated shipment delay, the Coordinator will notify the GSC-BC on-call personnel of the potential arrival of samples after normal working hours or on the weekend.
23. Upon receiving the cryoport, the temperature will be recorded and quality control verified by a second individual.
24. Any questions regarding shipments to the GSC-BC should be directed to the GSC-BC Coordinator at 604-877-6088.

GSC-BC Coordinator:

Jacqueline Schein
Genome Sciences Centre
BC Cancer Agency
Suite 100
570 West 7th Avenue
Vancouver, BC V5Z 4S6
Canada

Email: jschein@bcgsc.ca
Phone: 604-877-6088

Adopted:_____4/28/2010__
2nd Version :_____6/11/2010__
3rd Version :_____9/01/2010__
Reviewed:_____
4th Version :_____

SAMPLE SHIPPING GUIDELINES FOR THE HIV+ TUMOR MOLECULAR CHARACTERIZATION PROJECT

I. INTRODUCTION:

Tumor samples from HIV+ patients are rare and they may be accrued at specific tumor source sites (TSS) at a rate of 3-5 per calendar year. Shipping costs for infectious labeled material in vapor phase liquid nitrogen containers (cryoports) are expensive.

A. SCOPE AND PURPOSE:

1. To establish a sample shipping guideline standard to be applied to all samples contributed to the HIV+ Tumor Molecular Characterization Project (HTMCP), that balances the need for expeditious transport while maintaining cost efficiency.
2. This procedure applies to all TSSs.

II. ADOPTED STANDARD:

- Immediate requests for a cryoport will be made to the Genome Science Center at British Columbia (GSC-BC) coordinator when the contributing TSS has in its possession 3 or more matched tumor-normal tissues.
- However, if less than three cases are accrued, and the date of oldest sample resection is more than 4 months, shipment of this/these sample(s) is warranted.

Any questions regarding this protocol should be directed to Dr. Jean C. Zenklusen at 301-451-2144.

CONTACTS:
Project Team Representative:

Dr. Jean Claude Zenklusen
Scientific Programs Director
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-2144
Fax: 301-480-4368
e-mail: jz44m@nih.gov

GSC-BC Coordinator:

Jacqueline Schein
Genome Sciences Centre
BC Cancer Agency
Suite 100
570 West 7th Avenue
Vancouver, BC V5Z 4S6
Canada
Email: jschein@bcgsc.ca
Phone: 604-877-6088

Adopted:_____4/28/2010_
2nd Version :_____6/11/2010_
3rd Version :_____9/01/2010_
Reviewed:_____
4th Version :_____

SAMPLE IDENTIFIER STANDARDS FOR THE HIV+ TUMOR MOLECULARCHARACTERIZATION PROJECT

I. INTRODUCTION:

To assure the privacy of all human subjects that have consented to donate their tissues and clinical data to the HIV+ Tumor Molecular Characterization Project (HTMCP), all the materials given to the project must be de-identified prior to shipment and study. This project-assigned ID must have a rational structure that permits tracking of which subproject, tissue source site (TSS) and case is labeled.

A. SCOPE AND PURPOSE:

B. To establish a sample identifying standard to be applied to all samples and data contributed to the HTMCP.
C. This procedure applies to all laboratory personnel.

II. ADOPTED STANDARD:

- Samples contributed to the HTMCP must be labeled with a ID obtained from the Data Coordinating Center (DCC) by the TSS previous to shipment.
- These code must have the following form:

HTMCP - #### - ##### - ##X - X

Where:

1. HTMCP stands for HIV+ Tumor Molecular Characterization Project
2. The next 4 digits
    a. The first digit identifies the tumor type (1=DLBCL , 2=Lung)
    b. The next three digits identify the Tissue Source Site
3. The next five digits are the sample identifier
4. The last two digits specify sample type (01=Tumor, 10=Normal; 20=diagnostic update pathology report; 50=consensus pathology report)
5. First letter identifies the aliquote/section of the sample.
6. Letter identifies nucleic acid type (R=RNA, D=DNA)

Any questions regarding this protocol should be directed to Dr. Jean C. Zenklusen at 301-451-2144.

Adopted:_____6/25/2010_
2nd Version :_____9/01/2010_
3rd Version :_____
Reviewed:_____
4th Version :_____

DISPOSITION FORM FOR REMAINING MACROMOLECULES/TISSUES CONTRIBUTED TO THE HIV+ TUMOR MOLECULAR CHARACTERIZATION PROJECT

INTRODUCTION:

The HIV+ Tumor Molecular Characterization Project (HTMCP) is an initiative to compare the cancer related alterations in HIV+ patients and HIV- patients. The project aims to generate large scale, high quality data on the cancers' genome and transcriptome using 2nd generation sequencing technology which means that the changes identified range from large genomic rearrangements, expression profile changes and detection of mutations. The characterization of the latter is mostly performed in other NCI-sponsored projects. The comparison of alterations in transcriptomes and genomes of tumors from HIV^+ and HIV^- individuals may or may not identify a) virus-associated genomic alterations (including mutations) which would indicate if the etiology of the illness is different; and/or b) novel non-human sequences which could suggest the presence of transcripts from known or hitherto undiscovered oncogenic viral agents.

Tissues to the HTMCP are contributed by a number of international investigators (tissue source site, TSS). A major contributor is the AIDS Malignancy Consortium (AMC), a National Cancer Institute-supported clinical trials group founded in 1995 to support innovative trials for AIDS-associated malignancies. The AMC is composed of 14 Clinical Trials Sites and their affiliates, and is committed to enhancing therapeutic options for patients with HIV-associated malignancies. All samples and macromolecules obtained from cases contributed by AMC members are sent to the AIDS and Cancer Specimen Resource (ACSR, http://acsr.ucsf.edu/dotnetnuke/) for banking.

ACSR is a resource for investigators working in the fields of HIV/AIDS, cancer, virology, immunology, pathology, epidemiology, tumor biology assay development, and many others. It is a biorepository for HIV-infected human biospecimens from a wide spectrum of HIV-related or associated diseases, including cancer, and from appropriate HIV-negative controls. ACSR was established by the NCI in 1994 to acquire, store, and equitably distribute tumor tissues, biological fluids, and associated clinical information from patients with HIV-associated malignancies to the scientific research community-at-large. Availability of such biospecimens facilitates efforts to identify therapeutic targets and gain further insights into the pathogenesis and treatment of cancer in the HIV-infected population.

The ACSR's public access and research facilitation function makes it an ideal location to bank any remaining tissue and/or derived macromolecule after the molecular characterization is completed by the HTMCP.

SCOPE AND PURPOSE:

- To establish a procedure to follow for the disposition of remaining macromolecules (DNA and/or RNA) and tissue after characterization is completed from cases submitted to the HTMCP.
- This form must be completed by every TSS and included along with the shipping documents at the time of tissue submission **if the default option of banking at the ACSR is not acceptable**.

Remaining Material Disposition:

You only need to choose one of the options below if you do not want to send to ACSR for banking.

Should after molecular characterization of case # _____ be any remaining material (tissue and or macromolecules); these remnants should be (choose one):

- Sent back to the TSS (at the TSS's expense).
- Destroyed.

Name: Date:

Institution:

Signature:

Should you have any question please contact Dr. Zenklusen at 301-451-2144

Project Team Representative:

Dr. Jean Claude Zenklusen
Scientific Programs Director
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-2144
Fax: 301-480-4368
e-mail: jz44m@nih.gov

Adopted:_____
2º Version:_____
3º Version:_____
4º Version:_____
Under Revision:_____

VERY USEFUL INSTRUCTIONS ON HOW TO COMPLETE A STUDY PROTOCOL REQUEST TO THE INSTITUTIONAL REVIEW BOARD (IRB) FOR THE HIV+ TUMOR MOLECULAR CHARACTERIZATION PROJECT

INTRODUCTION:

The HIV+ Tumor Molecular Characterization Project's (HTMCP) goal is to develop a comprehensive database of the molecular changes in Human Immunodeficiency Virus (HIV)-associated cancers (from HIV-infected patients) that will be available to the research community world-wide. It will allow the comparison between the cancer related alterations in HIV+ patients and HIV- patients. The project aims to generate large scale, high quality data on the cancers' genomes and transcriptomes using 2nd generation sequencing technology which means that the changes identified range from large genomic rearrangements, expression profile changes and detection of mutations.

In order for cases to be included in the project, the patients must provide consent of participation in an approved IRB protocol specifying that the samples can be used for genomic characterization and that the data deposited in a publicly available, yet patient privacy designed database. The Office of Cancer Genomics of the National Cancer Institute has created a generic template that contains the appropriate language to help the Tissue Source Site (TSS) in producing the IRB document. This template lacks details that are Institution-specific and should not be considered complete.

SCOPE AND PURPOSE:

- To establish a set of instructions allowing each TSS to create their own IRB protocol to contribute samples to the HTMCP.
- These instructions should be useful to every TSS contributing samples to the HTMCP.

INSTRUCTIONS:

1. Obtain the IRB protocol template from either the SOP package sent when you agreed to participate in the HTMCP or the Sharepoint site (https://ocg-sps.nci.nih.gov/HIV_Tumors/default.aspx). You may also request a copy from the project team (see address below).

2. Fill in your organization name, PI's name and other pertinent information in the form. The Project name should be "HIV+ Tumor Molecular Characterization Project" and it's acronym is HTMCP.
3. The project rationale can be found in the introduction section of SOP#101.
4. The total number of samples that will be analyzed for each tumor type is 100.
5. Details on amount of tissue requested is in SOP#101 under the sample requirement section (page 8)
6. Details on the blood collection for germline DNA extraction can be found in SOP#103.
7. Cheek swabs will not be used as a source of normal DNA in this project; please delete that language in the template.
8. All the operational details of the project are clearly specified in the SOPs sent to the TSSs. It is expected that all participating personnel will read the SOPs, be familiar with the project procedures and requirements and follow them in all instances.

Should you have any question please contact Dr. Zenklusen at 301-451-2144

Project Team Representative:

Dr. Jean Claude Zenklusen
Scientific Programs Director
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-2144
Fax: 301-480-4368
e-mail: jz44m@nih.gov

Data Release Policy for the HIV+ Tumor Molecular Characterization Project (HTMCP)

Background:

Rapidly evolving sequencing and informatics tools are substantially diminishing costs of comprehensive characterization of tumor transcriptomes and tumor genomes. These advances have resulted in detailed information on the repertoire of alterations in tumors. NCI already supports tumor genome characterization projects for several common cancers, as part of the Cancer Genome Characterization Initiative and the Cancer Genome Atlas (TCGA). Comprehensive sequencing of genomes and transcriptomes in cancers that arise in HIV-infected individuals may provide a starting point for a systems biology approach towards understanding differences in etiologies among identical histological subtypes of cancers in HIV+ and HIV- patients. The results obtained could provide important clues to the pathways that either allow tumors to counteract immune surveillance mechanisms or are redundant in the presence of an extrinsic oncogenic influence such as viruses. It is also possible that the comparison of transcriptomes and genomes between tumors from HIV^+ and HIV^- individuals might identify novel non-human sequences that could suggest the presence of transcripts from hitherto undiscovered viral agents.

This is a "community resource project", with rapid data release to enable accelerated translation to enhance clinical impact. Therefore patenting on the PRIMARY data is discouraged to allow easy access and encourage its use. There is an expectation of a rapid initial "summary" publication by the group once the data are generated.

Two data types will be produced; 1) raw sequences from the tumor/normal genomes and tumor transcriptome, 2) analyzed data from those raw sequences. It is important to acknowledge that algorithms for sequence analysis to identify tumor-specific calls are still in the development stage and thus the results obtained require confirmation. Confirmation is defined in two ways:

- Verification: assessment of sequence quality before data release (e.g. identifying Illumina artifacts, performing sample swaps, etc.).
- Validation: confirmation of variants identified by the current analytical algorithms by using orthogonal experimental methodology such as Sanger sequencing. Validation will be performed; the scope will depend on the costs and the accuracy of the sequence-calling algorithms available at the specific time. It may be performed either for a subset or all variants found (the details will be developed on real time basis to take advantage of the best approaches). The criteria for selection of a subset of variants for validation will be developed by the cancer-specific working group based on all empirical data available at decision time.

Policy:

The data release policy should be consistent across all NCI-funded large-scale genomic characterization projects. The HIV+ cancers are hard to accrue and therefore the data generation

will span over a number of months or years. To best accomplish the goals of the project (generating and analyzing large enough data set to be able to draw statistically and biologically sound conclusions) and the Institute (to facilitate research and reduce redundancy by making primary data available to the scientific community in real time), the project members suggest the following policy:

- *Release of analyzed sequences (BAM files) will occur after a sample set (number to be determined) is complete, but not later than 4-6 month after they are generated.*
- *Table of the validated mutations (MAF) will be deposited to the Data Coordinating Center (DCC) after manuscript describing the findings of the dataset is submitted for publication.*

The DCC data portal (http://cgap.nci.nih.gov/cgci.html) will include a text about the philosophy of the rapid data release policy, "The Responsible use and publication of Data Generated by the Cancer Genome Characterization Initiative". The language will be aligned as much as possible to the one used for TCGA and Therapeutically Applicable Research to Generate Effective Treatments (TARGET).

An HIV+ tumor project manuscript(s) could include:

1. Commentary detailing the scientific aims and organization of HIV+ tumor molecular characterization project.
2. Analysis of paired DNA sequencing data for the sample set.
3. Analysis of the RNA sequencing data for the sample set.
4. Validation of a subset of variant calls found by either DNA or RNA sequencing of the sample set.

To support the continued prompt public release of large-scale genomic data prior to publication, researchers who plan to prepare manuscripts that would be comparable to the analyses described above, and journal editors who receive such manuscripts, are encouraged to coordinate their independent reports with the project's publication schedule described above. This may be done by contacting the Project Team (see below).

Once the first global analysis by the project members is in press, all other researchers are free, and indeed encouraged, to publish results based on integrating HIV+ tumor data with data from other sources. Researchers also are encouraged to use HTMCP data to publish on the development of novel methods to analyze genomic data related to cancer and genotype-phenotype relationships in cancer.

NCI does not consider that deposition of data from the HTMCP, like those from other large-scale genomic projects, into its own or public databases to be the equivalent of publication in a peer-reviewed journal. Therefore, although the data are available to others, the producers still consider them to be formally unpublished and expect that the data will be used in accord with standard scientific etiquette and practices concerning unpublished data.

Prior to the publication of the initial paper, the HTMCP project requests that authors who use

data acknowledge the H+TMCP as follows: *"The results published here are in whole or part based upon data generated by The HIV+ Tumor Molecular Characterization Project established by the Office of Cancer Genomics and Office of HIV and AIDS malignancies of the NCI. Information about project and the investigators and institutions that constitute the HIV+ Tumor workgroups can be found at http://cgap.nci.nih.gov/cgci.html)"*. After initial publication, the paper and website should be referenced.

To ensure protection of genetic privacy for sample donors, data users will have to agree to certain conditions described in the HTMCP Patient Protection Policy and Controlled Access Policy as to how the data will be used. For example, users will have to agree that they will share these data only with others who have also completed a data access agreement and that they will not patent discoveries in a way that prevents others from using the data. This means that reviewers of a manuscript who need to see any controlled-access HTMCP data underlying a result must also agree to these user access conditions before they can see these data.

Meeting presentations of HTMCP data and analyses by project team members are possible and encouraged. , We would request that the project team members inform the NCI of public meeting oral and poster presentations. The HTMCP Project Team will develop two-three slides that should be used for oral presentations, posters, etc. They will provide a standard method of citing the HTMCP and its many contributors; it is critical that the HTMCP also be properly cited and identified in the meeting abstracts, and language will also be provided to accomplish this goal.

Project Team Representative:

Dr. Jean Claude Zenklusen
Scientific Programs Director
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-2144
Fax: 301-480-4368
e-mail: jz44m@nih.gov

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THE HIV+ TUMOR MOLECULAR CHARACTERIZATION PROJECT
DIFFUSE LARGE B-CELL LYMPHOMA CONTACTS

Project Team Representative:

Dr. Jean Claude Zenklusen
Scientific Programs Director
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-2144
Fax: 301-480-4368
e-mail: jz44m@nih.gov

Data Coordinating Center:

Patee Gesuwan
MSC 8505
2115 E Jefferson St.
Rockville, MD 20892
Phone: 301-443-6147
E-mail: gesuwanp@mail.nih.gov

HIV+TMCP Pathology Coordinators:

Dr. John Chan MD
Amelia and Austin Vickery Professor of Pathology
Co-Director, Center for Lymphoma and Leukemia Research
University of Nebraska
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7689
Fax: 402-559-6018

E-mail: jchan@unmc.edu

OR

Dr. Kai Fu, MD, PhD
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7526
Fax: 402-559-6018
E-mail: kfu@unmc.edu

GSC-BC Coordinator:

Jacqueline Schein
Genome Sciences Centre
BC Cancer Agency
Suite 100
570 West 7th Avenue
Vancouver, BC V5Z 4S6
Canada
Email: jschein@bcgsc.ca
Phone: 604-877-6088

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HIV+ TUMOR MOLECULAR CHARACTERIZATION PROJECT
LUNG TUMOR CONTACT PERSONS

Project Team Representative:

Dr. Jean Claude Zenklusen
Scientific Programs Director
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-2144
Fax: 301-480-4368
e-mail: jz44m@nih.gov

Data Coordinating Center:

Patee Gesuwan
MSC 8505
2115 E Jefferson St.
Rockville, MD 20892
Phone: 301-443-6147
E-mail: gesuwanp@mail.nih.gov

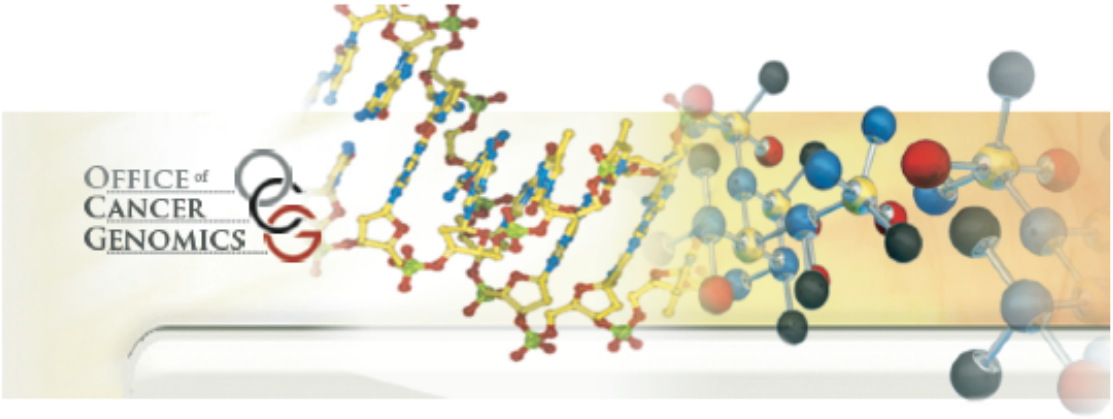
HIV+TMCP Pathology Coordinators:

Peter B Illei, MD
Assistant Professor of Pathology
Director of Immunopathology Laboratory
Johns Hopkins Medical Institutions
401 N. Broadway, Weinberg Bldg. Rm. 2242
Baltimore, MD 21231
Tel: 410-502-5160
Fax: 410-614-9663
e-mail: pillei1@jhmi.edu

GSC-BC Coordinator:

Jacqueline Schein
Genome Sciences Centre
BC Cancer Agency
Suite 100
570 West 7th Avenue
Vancouver, BC V5Z 4S6
Canada
Email: jschein@bcgsc.ca
Phone: 604-877-6088

National Cancer Institute



HTMCP DLBCL-SPECIFIC PROTOCOLS

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

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4th Version :_____

PROSPECTIVE SAMPLE SUBMISSION PROCEDURE FOR THE HIV+TUMOR MOLECULAR CHARACTERIZATION PROJECT

I. INTRODUCTION:

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Office of HIV and AIDS Malignancy (OHAM) have developed an initiative to compare the cancer related alterations in HIV+ patients and HIV- patients. It is possible that the comparison of transcriptomes and genomes between tumors from HIV^+ and HIV^- individuals may or may not identify novel non-human sequences which could suggest the presence of transcripts from known or hitherto undiscovered oncogenic viral agents.

A. SCOPE AND PURPOSE:

1. To establish a general procedure to inform personnel of all the steps necessary for a successful submission of a sample to the HIV+ Tumor Molecular Characterization Project (HTMCP).
2. This protocol applies to all Tissue Source Sites (TSSs) providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times and which samples were affected. This information should be given within 48 hours of the occurrence to the project team by sending an e-mail to Dr. Jean C. Zenklusen (**jz44m@nih.gov**) with the details.

II. PROCEDURES:

A. BEFORE PATIENT ACCRUAL BEGINS:

1. Make sure all the documents required for sample shipment as spelled out in SOP#100 are in place before you start case accruals.

B. BEFORE PATIENT SURGERY:

1. Create a TSS-assigned ID for your patient. Your institution will be the keeper of the key as described in your approved IRB protocol.
2. Contact the data coordinating center (DCC, see address below) with your TSS-assigned ID to obtain a project-assigned ID to use in all documents regarding the case and all materials shipped. **The TSS is responsible for maintaining the link between project-assigned ID and TSS-assigned ID in order to retrieve clinical information when required.** It is the TSSs responsibility to be able to track the patient's records back in the event that the original researcher(s) at the institution loose their affiliation.
3. Contact PT and obtain freezer-resistant labels that you should use to mark all containers/slides carrying materials for the project.
4. Make sure to prepare the tissue freezing station and have ready all the materials needed for tissue processing (HTMCP SOP #102).
5. Inform the research nurse that a 10ml peripheral blood sample must be obtained from the patient to use as non-tumoral control (see Appendix A). Store the blood sample in the refrigerator until processing (see HTMCP SOP #103, blood processing). Time in storage must be decided at site and reported back to Project Team.

C. DURING PATIENT SURGERY:

1. Inform the surgical staff of the tissue requirements for the project (see Appendix A).
2. Have a person ready to transport the ablated tissue to the processing station. It is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.

D. AFTER SURGERY:

1. Process solid tissue as described in the tissue processing protocol (HTMCP SOP #102). Timely processing is crucial, it is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.
2. Process blood sample according to protocol (see HTMCP SOP #103, blood processing). Store isolated cells in liquid nitrogen storage until shipment.
3. Obtain fifteen (15) unstained 4 μm sections from the formalin-fixed block (or the whole FFPE block). Affix one of the provided freezer-resistant labels to each slide or block.

E. PREPARING SAMPLES AND SHIPMENT:

1. Section frozen tumor sample following the frozen tissue sectioning protocol (HTMCP SOP #201A).
2. Contact the GSC-BC coordinator to obtain a cryoport transport vessel to ship the cryovials containing frozen tumor sample sections and frozen blood cells.

3. Once the cryoport arrives follow the frozen sample shipment protocol (HTMCP SOP #104) and send the frozen samples to the GSC-BC. On shipment, provide both the GSC-BC and PT with tracking number.
4. Send the fifteen (15) unstained 4 μm sections obtained from the formalin fixed blocks (or the whole block) to the pathology coordinator at UN. On shipment, provide both the pathology coordinator and PT with tracking number. For shipment use a closable box (such as Thermo Scientific* Plastic Slide Box, capacity 25 slides, catalog# B1780).
5. Collect all the clinical data requested in the sample requirements (Appendix A) and send electronically to the DCC.

NOTES:

- A checklist is provided to help you track all the steps required by this process (Appendix B). Please use it!
- If any one of the required items (institutional certification, confirmation of informed consent, frozen tissue, frozen blood cells, unstained slides and clinical data) is not present, the submission is incomplete and reimbursement of costs cannot proceed.
- **At no point in the process can traditionally-used identifying information (such as the patient name, address, phone number, medical record number, or social security number) be used to label samples. Only use the project-assigned ID and labels provided by the Project Team.**

APPENDIX A: Sample Requirements

HIV+Tumor Molecular Characterization Project
Tissue Sample Requirements for Accrual

Tissue Requirements:

To be accepted to the project, the following conditions have to be met at the tissue level.

- Paired tumor and normal (blood) must be available in sufficient quantities (see below).
- Tissues (both normal and tumor) need to be snap frozen. Time between tissue extraction and freezing must be recorded.
- Optimal storage of the tissues is in N_2(liq), but -80ºC or lower is acceptable. The form of tissue storage must be recorded.
- There must be enough tissue of both to produce a 4µm thick section from the top for H&E staining, then 10 sections of 20µm thickness, followed by another 4µm section to stain by H&E. **The number of sections needed is based on a block with a surface area of about one sq. cm. If the area is smaller, proportionately more sections will be required. See SOP #201A Tissue Sectioning Protocol for formula allowing calculation of number of sections needed.** A core biopsy obtained at the same time as the one produced for pathology might provide sufficient tissue if it is of high tumor content and low necrosis. Approximate tissue needed: 50 µg.
- Tumors need to have a minimum percent of tumor nuclei between 70-80% as assessed on an H&E section physically adjacent to the specimen that is candidate for generating the RNA and DNA.
- A paraffin embedded block for pathology consensus review must exist for the tumor.

HIV+TUMOR MOLECULAR PROJECT Characterization Project
Clinical Data Requirements for Accrual

Clinical Data Requirements:

To be accepted to the project, the following conditions must meet at the clinical data level. The samples must meet ALL the clinical data elements (CDEs) here listed.

These clinical data elements must be reported to the DCC as an initial report within two weeks of enrolling the patient. Updates must be sent to the DCC as the patient returns for periodic visits (ideally every 3-4 months).

- Patients need to be consented in such way that allows for the use of their tissues for genomic-scale molecular characterization.

Data element	Data type	Example
Unique identifier	text	XX-XXXX
WHO diagnosis	text	DLBCL
Date pathologic diagnosis	date (dd.mm.yyyy)	01.02.2003
Age at diagnosis	number	55
Gender	text	M
Race + Ethnicity (2 CDEs, CDC/Census std)		
Stage (Ann Arbor)	text	4A
Stage (limited vs. advanced)	text	LIM
Performance status (ECOG)	text	1
Lactate dehydrogenase level (LDH) (as ratio of measured value/upper limit of normal)	number	1.3
Hemoglobin (g/L)	number	133
Sites of extranodal disease	text	bone marrow, lung
Largest tumor mass diameter (cm)	number	8
International prognostic index (IPI) score	number	3
Primary treatment	text	CHOP-R
Primary treatment start date		
Response to primary treatment	text	Complete

Date of assessment of response		
Date progressive disease, if occurred	date (dd.mm.yyyy)	11.11.2005
Primary site of progression	text	Lung
Secondary treatment	text	GDP
Secondary treatment start date		
Hematopoietic stem cell transplant (HSCT) (yes/no)	text	Yes
Date HSCT	date (dd.mm.yyyy)	03.01.2006
Date last follow-up	date (dd.mm.yyyy)	11.11.2006
Status at last follow-up (alive/dead)	text	Dead
Number of months from diagnosis to last follow-up (living patients only)	number	
Cause of death	text	lymphoma
Date of death		
Onto a trial after Secondary?	boolean	
Trial ID		
Other fields for consideration:		
Prior Dx for LPL/WM?		
Uric acid test		
Surface antigens, IHC, CD		
HIV Related Data		
Date of HIV diagnosis, if known	Text mm/yyyy	
Nadir CD4 counts	number cells/mm^3	
CD4 counts at lymphoma diagnosis	number cells/mm^3	
HIV RNA load at lymphoma diagnosis	copies/ml	
Prior AIDS defining co-morbidities	Text Y/N	
Co-infections- serology data/viral load if available	Text Y/N	

HBV HCV KSHV		
HAART treatment prior to Lymphoma diagnosis	Text Y/N	
HAART treatment at time of lymphoma diagnosis	Y/N Drugs usedText	
HIV risk group(s)	Text Y/N	
History of other malignancies		

APPENDIX B: Checklist of Task Completion for Sample Submission

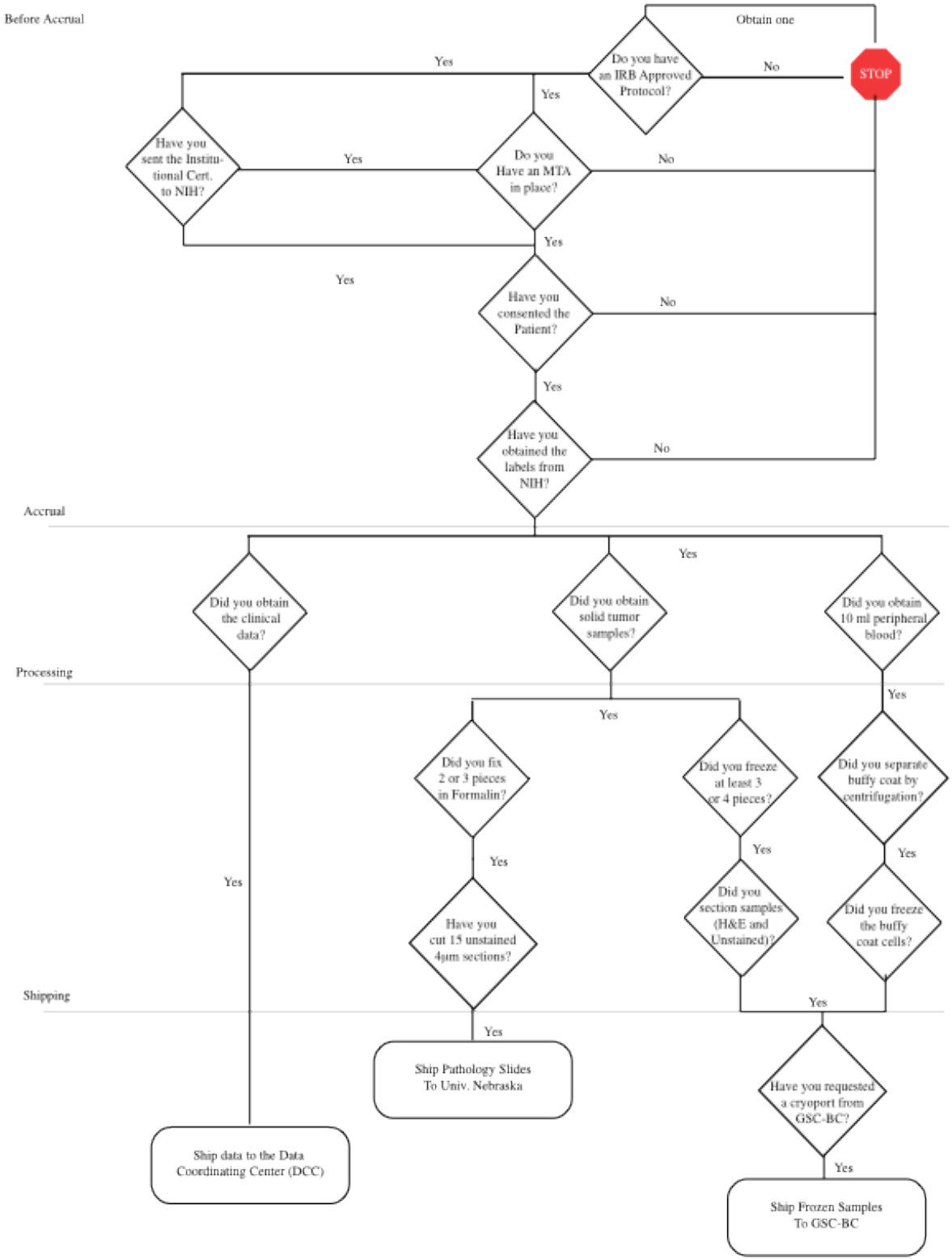
Date:
Institution:
Operator:

- ❖ Do you have an IRB approved protocol?
- ❖ Have you consented the patient?
- ❖ Have you sent your Institutional Certification to the Project Team?

- ❖ Have you obtained the project-assigned ID and labels from the Project Team?

- ❖ Do you have frozen sections in cryovial and H&E stained slides? Are they labeled?
- ❖ Do you have frozen blood cells? Are they correctly labeled?
- ❖ Have you secured a cryoport from the Genome Science Center at British Columbia?
- ❖ Do you have (15) unstained 4 μm sections from the Formalin-fixed block? Are they labeled?
- ❖ Do you have the clinical data elements required by the Project? (Appendix B)

ONLY if all the above items check out, you are ready to ship the samples.


Before Accrual
Obtain one
Do you have an IRB Approved Protocol?
No
STOP
Yes
Yes
Have you sent the Institutional Cert. to NIH?
Yes
Do you Have an MTA in place?
No
Yes
Yes
Have you consented the Patient?
No
Yes
Have you obtained the labels from NIH?
No
Accrual
Yes
Did you obtain the clinical data?
Did you obtain solid tumor samples?
Did you obtain 10 ml peripheral blood?
Processing
Yes
Yes
Did you fix 2 or 3 pieces in Formalin?
Did you freeze at least 3 or 4 pieces?
Did you separate buffy coat by centrifugation?
Yes
Yes
Yes
Yes
Have you cut 15 unstained 4µm sections?
Did you section samples (H&E and Unstained)?
Did you freeze the buffy coat cells?
Shipping
Yes
Yes
Yes
Ship Pathology Slides To Univ. Nebraska
Have you requested a cryoport from GSC-BC?
Yes
Ship data to the Data Coordinating Center (DCC)
Ship Frozen Samples To GSC-BC

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4th Version :_____

CENTRALIZED PATHOLOGY REVIEW PROCESS FOR HIV+ TUMOR MOLECULAR CHARACTERIZATION PROJECT

INTRODUCTION:

Pathological diagnosis of tumor can be impacted by the subjective nature of the process as well as the subjective definition of the criteria used in the assessment. To assure that samples entering the sequencing pipeline of the HIV+ Tumor Molecular Characterization Project meet the tissue requirements (set forth in SOP#101A) and are diagnosed as Diffuse Large B-cell Lymphoma, DLBCL, a central pathology review panel of five board-certified pathologists is established. The review of tissues by a group minimizes the subjectivity encountered in pathology practice.

A. SCOPE AND PURPOSE:

1. To establish a standard procedure to follow for the centralized pathology review of tissue submitted to the HIV+ Tumor Molecular Characterization Project.

B. EQUIPMENT AND MATERIALS:

1. De-identified pathology report provided by the tissue source site (TSS) contributing the sample.
2. Fifteen (15) unstained 4 μm thick sections from the formalin-fixed paraffin-embedded (FFPE) diagnostic block (or whole FFPE block). These sections will be provided by the tissue source site (TSS) contributing the sample labeled with the project-assigned ID (as specified in SOP #101 and 102).
3. Bioimagene Slide Scanner

II. PROCEDURE:

A. Preparation for review:

1. All members of a centralized pathology board obtain their Pathxchange credentials by going to the following website: http://www.pathxchange.org/user/register
2. Once the credentials are secured, they should be communicated to the appropriate OCG project manager.
3. Immediately upon arrival to the pathology center, the pathology coordinator will verify that all slides and report submitted are labeled with the same project-assigned ID.

- The report will be scanned and PathXchange website (http;//www.pathxchange.org).

4. Pathology coordinator will send the appropriate number of slides to the histology service to perform hematoxylin & eosin (H&E) as well as necessary immunohistochemical (IHC) and in situ hybridization procedures.
   - IHC to be performed include: **CD3, CD10, CD20, BCL6, MUM1, BCL2, Ki67, TP53 , CD79a.**
   - In situ hybridization will be performed: **EBER**.
   - The processing should take no longer than 5 days.
5. After all the processing is completed, the pathology coordinator will scan the slides on the Bioimagene system.
6. Images of the IHC slides and a blank review form will be deposited in the PathXchange website (http;//www.pathxchange.org) by the pathology coordinator.
7. The coordinator will send an e-mail to the members of the PRC informing them that materials for review have been deposited in a folder. This communication must specify the number and name of files, as well as the project-assigned ID for the case(s) under review. This deposition and communication must occur within 48 hours of scanning the slides by the pathology coordinator.

B. Review:
   1. Within a three days of receipt of the e-mail from the coordinator, all members of the PRC will return their pathology review form to the pathology coordinator via e-mail.
   2. If a consensus, 3 out of 4 reviewers for the DLBCL cases, is reached and the case passes the specified criteria the pathology coordinator will create a final pathology report and submit it to the Data Coordinating Center and the Genome Science Center at British Columbia (GSC-BC) so they will start the sequencing of that case(s).
   3. Cases considered inadequate for diagnosis will be labeled as such and taken out of the study.
   4. Discrepant cases will be submitted for a web-based consensus review, to be convened by Dr. Stefania Pittaluga. The schedule of such consensus reviews will be dictated by the number of discordant cases accrued as follows:
      - When 6 or more discordant cases have been accrued, a consensus review panel must be convened.
      - If there are less than 6 discordant cases, but the oldest accrued case is more than six months old, a consensus review panel must be convened.

Any questions regarding this protocol should be directed to the HIV+TMCP Pathology Coordinators at 402-559-7689 or 402-559-7526.

CONTACTS:
Project Team Representative:

Dr. Jean Claude Zenklusen
Scientific Programs Director
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-2144
Fax: 301-480-4368
e-mail: jz44m@nih.gov

Data Coordinating Center:

Patee Gesuwan
MSC 8505
2115 E Jefferson St.
Rockville, MD 20892
Phone: 301-443-6147
E-mail: gesuwanp@mail.nih.gov

HIV+TMCP Pathology Coordinators:

Dr. John Chan MD
Amelia and Austin Vickery Professor of Pathology
Co-Director, Center for Lymphoma and Leukemia Research
University of Nebraska
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7689
Fax: 402-559-6018
E-mail: jchan@unmc.edu

OR

Dr. Kai Fu, MD, PhD
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center

668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7526
Fax: 402-559-6018
E-mail: kfu@unmc.edu

GSC-BC Coordinator:

Jacqueline Schein
Genome Sciences Centre
BC Cancer Agency
Suite 100
570 West 7th Avenue
Vancouver, BC V5Z 4S6
Canada
Email: jschein@bcgsc.ca
Phone: 604-877-6088

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Reviewed:_____
4th Version :_____

SECTIONING TISSUE FOR THE HIV+ TUMOR MOLECULAR CHARACTERIZATION PROJECT

I. INTRODUCTION:

A. SCOPE AND PURPOSE:

1. To establish a common procedure for tissue sectioning previous to shipment to the Genome Science Center at British Columbia (GSC-BC) across tissue source sites (TSS).
2. This protocol applies to all TSSs providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times and which samples were affected. This information should be given within 48 hours of ocurrence to the project team by sending an e-mail to Dr. Jean C. Zenklusen (**jz44m@nih.gov)** with the details.

B. SAFETY PRECAUTIONS:

1. Wear personal protective equipment (PPE) such as lab coats and gloves.

C. EQUIPMENT AND MATERIALS:

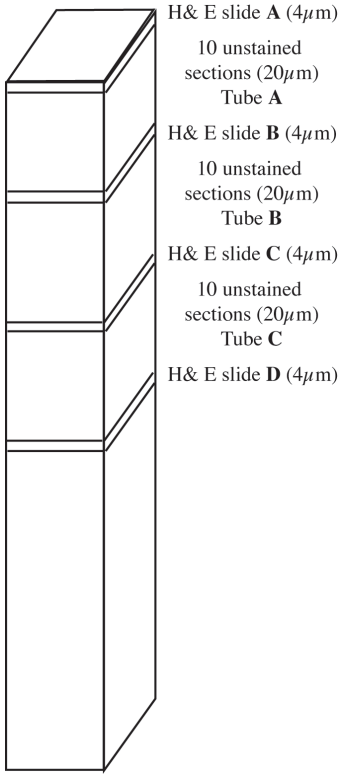
1. Personal protective equipment (PPE) to include heavy duty gloves, eye protection (preferably Face Shield), lab coat and closed-toe shoes
2. Frozen sample
3. OCT Freezing Compound
4. Cryostat
5. Glass slide(s) (such as Corning Glass Slides, 3 x 1" frosted end, # 26003)
6. Cryovials (2mL vials, e. g., ChartBiomed, Part Number 10778828)
7. Freezer resistant labels with project-assigned ID (obtained from Project Team, see HTMCP SOP #101A)

MARK ALL CONTAINERS WITH THE LABELS CARRYING PATIENT PROJECT-ASSIGNED ID OBTAINED PRIOR TO SURGERY.

II. PROCEDURE:

A. When preparing a tissue block for shipment to the GSC-BC the following steps must be followed:

1. All tube(s) must be kept in dry ice at all times and be stored in liquid nitrogen storage tanks until shipment to the GSC-BC can be arranged following the HTMCP Shipping Protocol (HTMCP SOP #105)
2. Transport the cryovial containing the sample on dry ice to the cryostat.
3. Remove Frozen tissue from cryovial with a clean pair of forceps (e.g., by washing them in 70% Ethanol).
4. Coat the top of the tissue piece with a thin layer of OCT by dipping into the compound held in a small weighing boat or similar container.
5. Obtain a 4um section and stain with H&E to assess the quality of the tissue (i.e, is the tumor percent nuclei greater than 70%). Label with the project-assigned ID and a capital letter A (e.g., HTCP-###-#####-##-A) and save the section for shipment.
   No sample should be shipped if the preliminary % tumor nuclei assessment at the TSS is below the 70% cut-off.
6. Label a cryovial with the project-assigned ID and a capital letter A (e.g., HTCP-###-#####-##-A). Cut ten 20um thick sections and put into a cryovial in a beaker of dry ice inside the cryostat. **The number of sections needed is based on a tissue with a surface area of about one sq. cm. If the area is smaller, proportionately more sections will be required and vice versa (see calculation formula below to estimate the number of sections needed)**
7. Coat the top of the tissue piece with a thin layer of OCT by dipping into the compound held in a small weighing boat or similar container.
8. Obtain a 4um section and stain with H&E to assess the quality of the tissue. Label with the project-assigned ID and a capital letter B (e.g., HTCP-###-#####-##-B) and save the section for shipment (see figure).



9. Additional sections (10/tube) may be cut into tubes B, C, etc. depending on the anticipated future research needs. A 4 um section must be obtained and stain with H&E to assess the quality of the tissue in between each series of thick sections. These H&E slides must be shipped to the appropriate location.
10. Return the remaining tissue to the liquid nitrogen storage tank.
11. **The blade should be cleaned with alcohol after each case and different parts of the blade used for different cases.**

12. Note that excess OCT must be carefully trimmed away before sectioning as its inclusion will interfere with subsequent RNA extraction.
13. Shipping institutions for the cryovials containg the frozen sections as well as the H&E sections are in the HIV+ Tumor Molecular Characterization Project Protocol (HTMCP SOP #101A)

B. Any questions regarding this protocol should be directed to the HTMCP Pathology Coordinators at 402-559-7689 or 402-559-7526.

THE FROZEN SPECIMENS SHOULD BE KEPT FROZEN ON DRY ICE AT ALL TIMES DURING TRANSPORT TO AND FROM STORAGE TANKS.

Estimating the number of 20µm sections needed:

1) Measure, in millimeters, the length and width of the tissue in the block.
2) Use the formula below to estimate the number of 20µm sections needed per cryovial to fulfill tissue requirements. Use that number of sections in step 6 of this protocol.

Number of sections = [Length (mm) x width (mm)] x 10 / 100 mm^2

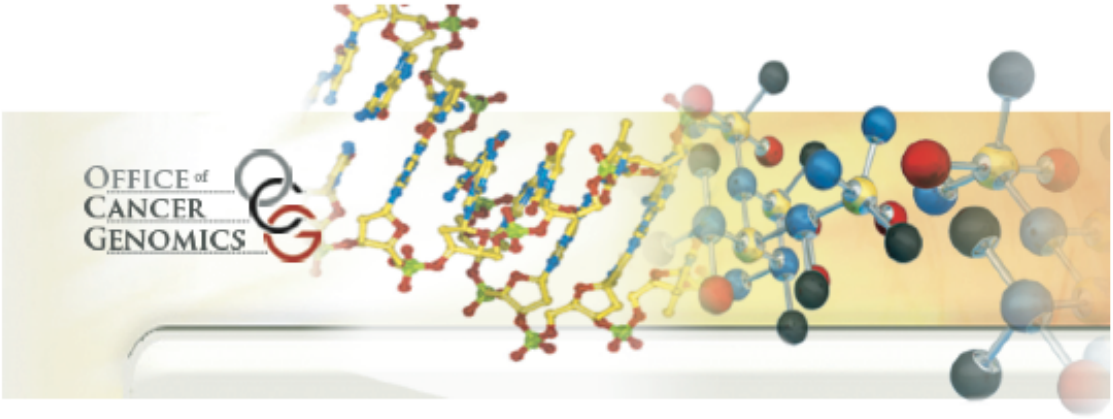
HIV+TMCP Pathology Coordinators:

Dr. John Chan MD
Amelia and Austin Vickery Professor of Pathology
Co-Director, Center for Lymphoma and Leukemia Research
University of Nebraska
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7689
Fax: 402-559-6018
E-mail: jchan@unmc.edu

OR

Dr. Kai Fu, MD, PhD
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7526
Fax: 402-559-6018
E-mail: kfu@unmc.edu

National Cancer Institute



HTMCP LUNG-SPECIFIC PROTOCOLS

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

Adopted:_____09/14/2010__
2º Version:_____
3º Version:_____
4º Version:_____
Under Revision:_____

PROSPECTIVE SAMPLE SUBMISSION PROCEDURE FOR THE HIV+ LUNG PROJECT

I. INTRODUCTION:

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Office of HIV and AIDS Malignancy (OHAM) have developed an initiative to compare the cancer related alterations in HIV+ patients and HIV- patients. It is possible that the comparison of transcriptomes and genomes between tumors from HIV^+ and HIV^- individuals may or may not identify novel non-human sequences which could suggest the presence of transcripts from known or hitherto undiscovered oncogenic viral agents.

A. SCOPE AND PURPOSE:

1. To establish a general procedure to inform personnel of all the steps necessary for a successful submission of a sample to the HIV+ Tumor Molecular Characterization Project (HTMCP).
2. This protocol applies to all Tissue Source Sites (TSSs) providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times and which samples were affected. This information should be given within 48 hours of the occurrence to the project team by sending an e-mail to Dr. Jean C. Zenklusen (**jz44m@nih.gov**) with the details.

II. PROCEDURES:

A. BEFORE PATIENT ACCRUAL BEGINS:

1. Make sure all the documents required for sample shipment as spelled out in SOP#100 are in place before you start case accruals.

B. BEFORE PATIENT SURGERY:

1. Create a TSS-assigned ID for your patient. Your institution will be the keeper of the key as described in your approved IRB protocol.

2. Contact the data coordinating center (DCC, see address below) with your TSS-assigned ID to obtain a project-assigned ID to use in all documents regarding the case and all materials shipped. **The TSS is responsible for maintaining the link between project-assigned ID and TSS-assigned ID in order to retrieve clinical information when required.** It is the TSS's responsibility to be able to track the patient's records back in the event that the original researcher(s) at the institution lose their affiliation.
3. Contact PT and obtain freezer-resistant labels that you should use to mark all containers/slides carrying materials for the project.
4. Make sure to prepare the tissue freezing station and have ready all the materials needed for tissue processing (HTMCP SOP #102).
5. Inform the research nurse that a 10 ml peripheral blood sample must be obtained from the patient to use as a non-tumoral malignant control (see Appendix A). Note that the plasma should be processed and the buffy coat should be separated from the plasma within two hours of being obtained from the patient. Storage of the buffy coat sample should then occur in a -80°C freezer.

C. DURING PATIENT SURGERY:

1. Inform the surgical staff of the tissue requirements for the project (see Appendix A).
2. Have a person ready to transport the ablated tissue to the processing station. It is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.

D. AFTER SURGERY:

1. Process solid tissue as described in the tissue processing protocol (HTMCP SOP #102). Timely processing is crucial, it is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.
2. Process blood sample according to protocol (see HTMCP SOP #103, blood processing). Store isolated cells in liquid nitrogen storage until shipment.
3. Obtain **five** unstained 4 μm sections from the formalin-fixed block (or the whole block). Affix one of the provided freezer-resistant labels to each slide or block.

E. PREPARING SAMPLES AND SHIPMENT:

1. Produce a 4μm frozen section of the top of the tumor sample for initial quality control as described in the tissue processing protocol (HTMCP SOP #102).
2. Contact the GSC-BC coordinator to obtain a cryoport transport vessel to ship the cryovials containing frozen tumor sample sections and frozen blood cells.
3. Once the cryoport arrives follow the frozen sample shipment protocol (HTMCP SOP #104) and send the frozen samples to the GSC-BC. On shipment, provide both the GSC-BC and PT with tracking number.

4. Send the **five** unstained 4 μm sections obtained from the formalin fixed blocks (or the whole block) to the pathology coordinator. On shipment, provide both the pathology coordinator and PT with the tracking number. For shipment use a closable box (such as Thermo Scientific* Plastic Slide Box, capacity 25 slides, catalog# B1780).
5. Collect all the clinical data requested in the sample requirements (Appendix A) and send electronically to the DCC using the appropriate TSS-assigned ID.

NOTES:

- A checklist is provided to help you track all the steps required by this process (Appendix C). Please use it!
- If any one of the required items (institutional certification, confirmation of informed consent, frozen tissue, frozen blood cells, unstained slides and clinical data) is not present, the submission is incomplete.
- **At no point in the process can traditionally-used identifying information (such as the patient name, address, phone number, medical record number, or social security number) be used to label samples. Only use the project-assigned ID and labels provided by the Project Team.**

APPENDIX A: Sample Requirements

HIV+ Lung Cancer Characterization Project
Tissue Sample Requirements for Accrual

Tissue Requirements:

To be accepted to the project, the following conditions have to be met at the tissue level.

- Paired tumor and normal tissue or plasma buffy coat must be available in sufficient quantities (see below).
- Tissues (both normal and tumor) need to be snap frozen. Time between tissue extraction and freezing must be recorded.
- Optimal storage of the tissues is in N_2(liq), but -80ºC or lower is acceptable. The form of tissue storage must be recorded.
- There must be 100 mg of tumor tissue with a minimum percent of tumor nuclei between 70-80% as assessed on an H&E section physically adjacent to the specimen that is candidate for generating the RNA and DNA.
- A paraffin embedded block for pathology consensus review must exist for the tumor.

HIV+ Lung Cancer Characterization Project
Clinical Data Requirements for Accrual

Clinical Data Requirements:

To be accepted to the project, the following conditions must meet at the clinical data level. The samples must meet ALL the clinical data elements (CDEs) here listed.

These clinical data elements must be reported to the DCC as an initial report within two weeks of enrolling the patient. Updates must be sent to the DCC as the patient returns for periodic visits (ideally every 3-4 months).

- Patients need to be consented in such way that allows for the use of their tissues for genomic-scale molecular characterization.

Data Element Label	Entry Options
Organ of Origin	Lung Lymph Node (metastatic tumor in regional lymph node)
Diagnosis	Squamous Cell Carcinoma (if checked, please fill out question #3) Adenocarcinoma (if checked, please fill out question #4)
Histological Subtype	(SCC) Squamous Cell Carcinoma, Not Otherwise Specified (NOS) Papillary Squamous Cell Clear Cell Squamous Cell Small Cell Squamous Cell Basaloid Squamous Cell
	(Adenocarcinoma)
	Adenocarcinoma, Not Otherwise Specified (NOS) Fetal Adenocarcinoma Mucinous Cystadenocarcinoma Mucinous (“Colloid”) Carcinoma Signet Ring Adenocarcinoma Clear Cell Adenocarcinoma Adenosquamous

	Large Cell carcinoma Carcinomas with pleomorphic, sarcomatoid or sarcomatous elements Carcinomas of salivary-gland type NSCLC (NOS)
	Neuroendocrine tumors Typical carcinoid Atypical carcinoid Small Cell Lung Cancer
Anatomic Organ Sub-Division	Lung R Upper Middle Lower L Upper Lower Bronchial Mediastinal
Gender	Male Female
Date of Birth	
Race	American Indian or Alaska Native *(A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment)* Asian *(A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam)* White *(A person having origins in any of the original peoples of Europe, the Middle East, or North Africa)* Black or African American *(A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American.")* Native Hawaiian or other Pacific Islander *(A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands)* Not Reported *(Not provided or available)* Unknown *(Could not be determined or unsure)*
Ethnicity	Not Hispanic or Latino *(A person not meeting the definition for Hispanic or Latino)*

	Hispanic or Latino *(A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin, regardless of race)* Not Reported *(Not provided or available)* Unknown *(Could not be determined or unsure)*
History of Prior Malignancy	Yes No Unknown
Date of Pathological Diagnosis	
Method of initial pathologic diagnosis	Cytology Fine needle aspiration biopsy Incision biopsy Excisional biopsy Tumor resection Other method, specify below
Other Method of Initial Pathologic Diagnosis	_____
Neo-adjuvant (prior to tissue procurement) Therapy **(If yes, this is an exclusion criterion)**	Yes No
Surgical Resection Date	
Residual Tumor	Not Applicable RX R0 R1 R2
Pathologic Spread: Pathologic Tumor **(pT)**	Not Applicable TX T0 Tis T1 T1a T1b T2

	T2a T2b T3 T4
Pathologic Spread: Regional Nodes **(pN)**	Not Applicable NX N0 N1 N2 N3
Pathologic Spread: Distant Metastasis **(M)** (Clinical or Pathologic)	M0 M1 M1a M1b
Tumor Stage (Pathologic)	IA IB IIA IIB IIIA IIIB IV
Date of Last Contact (if deceased, equals date of death)	
Date Last Known Alive	
Vital Status	Living Deceased
Tumor Status	Tumor Free With Tumor Unknown Tumor Status
Date of Death	Not Applicable
Karnofsky Performance Status Score:	100 Normal, no complaints, no evidence of disease 90 Able to carry on normal activity; minor signs or symptoms of disease 80 Normal activity with effort; some signs or symptoms of disease

	70 Cares for self, unable to carry on normal activity or to do active work 60 Requires occasional assistance, but is able to care for most of his/her needs 50 Requires considerable assistance and frequent medical care 40 Disabled, requires special care and assistance 30 Severely disabled, hospitalization indicated. Death not imminent 20 Very sick, hospitalization indicated. Death not imminent 10 Moribund, fatal processes progressing rapidly 0 Dead Unknown
Performance Status Scale**: Eastern Cooperative Oncology Group (ECOG)**	0 Asymptomatic 1 Symptomatic but fully ambulatory 2 Symptomatic but in bed less than 50% of day 3 Symptomatic, in bed more than 50% of the day 4 Bed ridden Unknown
Performance Status Score: **Timing**	Preoperative Pre-adjuvant therapy Post-adjuvant therapy Other Unknown
Tobacco smoking history indicator	Lifelong Non-smoker (<100 cigarettes in lifetime) Current smoker: includes daily smokers and non-daily smokers (or occasional smokers) Current reformed smoker for > 15 years Current reformed smoker for < 15 years
Age of onset tobacco smoking	___ ___ years

Year of quitting tobacco smoking	__ __ __ __ (YYYY)
Number of Pack Years Smoked	___ ___ ___ ___ pack years

HIV Related Data	
Date of HIV diagnosis, if known	Text mm/yyyy
Nadir CD4 counts	number cells/mm^3
CD4 counts at lung cancer diagnosis	number cells/mm^3
HIV RNA load at lung cancer diagnosis	copies/ml
Prior AIDS defining co-morbidities	Text Y/N
Co-infections- serology data/viral load if available HBV HCV KSHV	Text Y/N
HAART treatment prior to lung cancer diagnosis	Text Y/N
HAART treatment at time of lung cancer diagnosis	Y/N Drugs usedText
HIV risk group(s)	Text Y/N
History of other malignancies (by definition, this should be none, but I think it is good to keep this question here)	

APPENDIX B: Checklist of Task Completion for Sample Submission

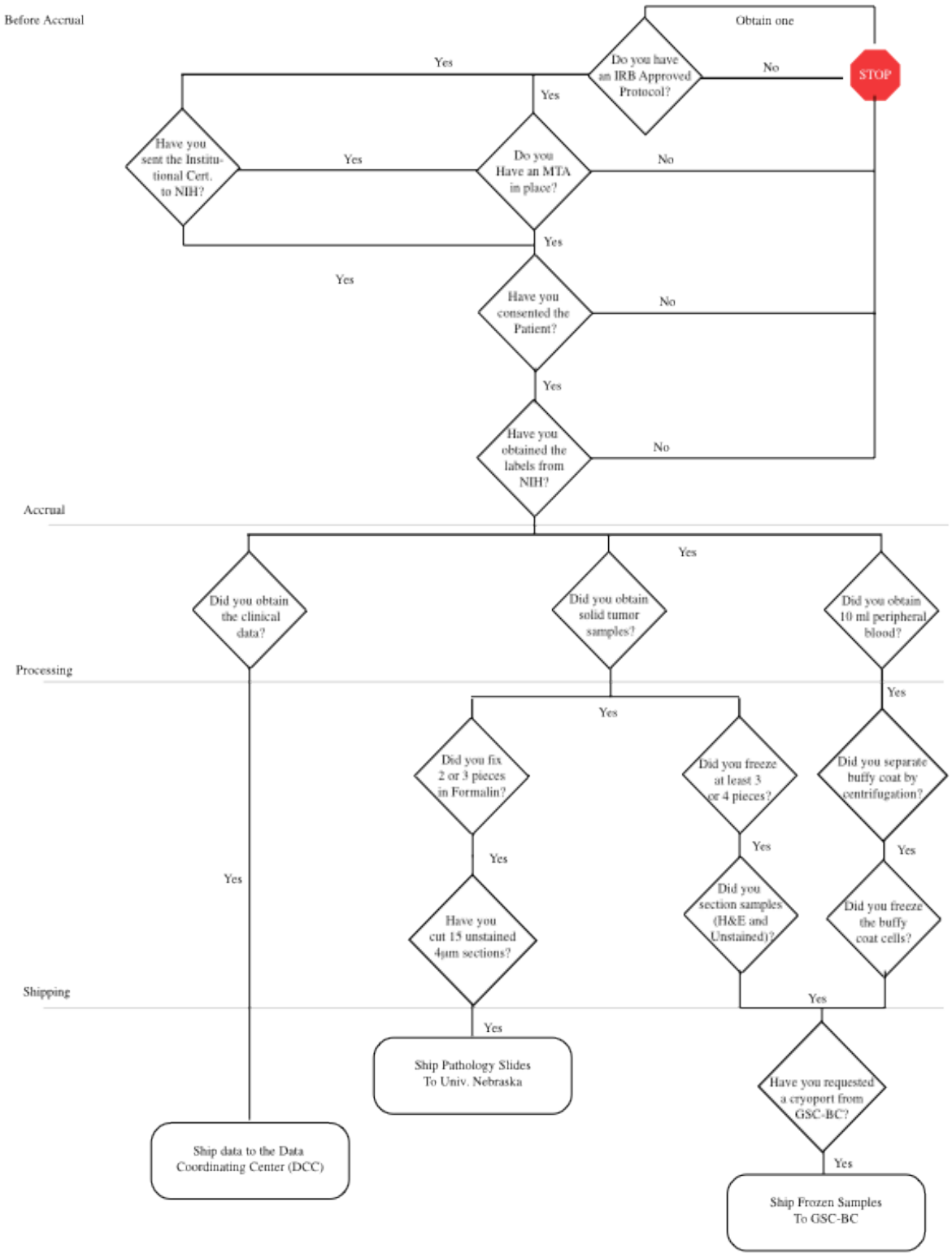
Date:
Institution:
Operator:

- ❖ Do you have an IRB approved protocol?
- ❖ Have you consented the patient?
- ❖ Have you sent your Institutional Certification to the Project Team?

- ❖ Have you obtained the project-assigned ID and labels from the Project Team?

- ❖ Do you have frozen sections in cryovial and H&E stained slides? Are they labeled?
- ❖ Do you have frozen plasma derived white blood cells? Are they correctly labeled?
- ❖ Have you secured a cryoport from the Genome Science Center at British Columbia?
- ❖ Do you have (5) unstained 4 μm sections from the Formalin-fixed block? Are they labeled?
- ❖ Do you have the clinical data elements required by the Project? (Appendix B)

ONLY if all the above items check out, you are ready to ship the samples.


Before Accrual
Obtain one
Do you have an IRB Approved Protocol?
No
STOP
Yes
Yes
Have you sent the Institutional Cert. to NIH?
Yes
Do you Have an MTA in place?
No
Yes
Yes
Have you consented the Patient?
No
Yes
Have you obtained the labels from NIH?
No
Accrual
Yes
Did you obtain the clinical data?
Did you obtain solid tumor samples?
Did you obtain 10 ml peripheral blood?
Processing
Yes
Yes
Did you fix 2 or 3 pieces in Formalin?
Did you freeze at least 3 or 4 pieces?
Did you separate buffy coat by centrifugation?
Yes
Yes
Yes
Yes
Did you section samples (H&E and Unstained)?
Did you freeze the buffy coat cells?
Shipping
Yes
Yes
Have you cut 15 unstained 4µm sections?
Yes
Ship Pathology Slides To Univ. Nebraska
Have you requested a cryoport from GSC-BC?
Yes
Ship Frozen Samples To GSC-BC
Ship data to the Data Coordinating Center (DCC)

Adopted:_____09/14/2010__
2º Version:_____04/07/2011__
3º Version:_____
4º Version:_____
Under Revision:_____

CENTRALIZED PATHOLOGY REVIEW PROCESS FOR HIV+ LUNG TUMORS

INTRODUCTION:

Pathological diagnosis of tumor can be impacted by the subjective nature of the process as well as the subjective definition of the criteria used in the assessment. To ensure that samples entering the sequencing pipeline of the HIV+ Tumor Characterization Project meet the tissue requirements (set forth in SOP#101) and are diagnosed as Lung Cancer, a central pathology review panel of three board-certified pathologists will be established. The review of tissues by a group minimizes the subjectivity encountered in pathology practice.

A. SCOPE AND PURPOSE:

1. To establish a standard procedure to follow for the centralized pathology review of tissue submitted to the HIV+ Tumor Characterization Project.

B. EQUIPMENT AND MATERIALS:

1. De-identified pathology reports provided by the tissue source site (TSS) contributing the sample.
2. Five unstained 4 μm thick sections from the formalin-fixed paraffin-embedded (FFPE) diagnostic block (or the whole FFPE block). These sections will be provided by the tissue source site (TSS) contributing the sample labeled with the project-assigned ID (as specified in SOP #101B and 102).
3. Bioimagene Slide Scanner

II. PROCEDURE:

A. Preparation for review:

1. All members of a centralized pathology board obtain their Pathxchange credentials by going to the following website: http://www.pathxchange.org/user/register
2. Once the credentials are secured, they should be communicated to the appropriate OCG project manager.
3. Immediately upon arrival to the pathology core, the pathology coordinator will verify that all slides and reports submitted are labeled with the same project-assigned ID.
    - The report will be scanned and PathXchange website (http;//www.pathxchange.org).

4. Pathology coordinator will send the appropriate number of slides to the histology service to perform hematoxylin & eosin (H&E) as well as necessary immunohistochemical (IHC) and in situ hybridization procedures.
   - IHC to be performed include: **TTF-1, p63**
   - In situ hybridization will be performed: **ALK FISH/HPV**.
   - The processing should take no longer than 5 days.
5. After all the processing is completed, the pathology coordinator will scan the slides on the Bioimagene system.
6. Images of the IHC slides and a blank review form will be deposited in the PathXchange website (http;//www.pathxchange.org) by the pathology coordinator.
7. The coordinator will send an e-mail to the members of the PRC informing them that materials for review have been deposited in a folder. This communication must specify the number and name of files, as well as the project-assigned ID for the case(s) under review. This deposition and communication must occur within 48 hours of scanning the slides by the pathology coordinator.

B. Review:
1. Within a three days of receipt of the e-mail from the coordinator, all members of the PRC will return their pathology review form to the pathology coordinator via e-mail.
2. The tumors will be classified using to the WHO classification
3. If a consensus, 3 out of 4 reviewers for the lung cancer cases, is reached and the case passes the specified criteria the pathology coordinator will create a final pathology report and submit it to the Data Coordinating Center and the Genome Science Center at British Columbia (GSC-BC) so they will start the sequencing of that case(s).
4. Cases considered inadequate for diagnosis will be labeled as such and taken out of the study.
5. Discrepant cases will be submitted for a web-based consensus review, to be convened by Dr. Peter Illei. The schedule of such consensus reviews will be dictated by the number of discordant cases accrued as follows:
   - When 6 or more discordant cases have been accrued, a consensus review panel must be convened.
   - If there are less than 6 discordant cases, but the oldest accrued case is more than six months old, a consensus review panel must be convened.

Any questions regarding this protocol should be directed to the HTMCP Pathology Coordinator at 410-502-5160

CONTACTS:
Project Team Representative:

Dr. Jean Claude Zenklusen
Scientific Programs Director
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-2144
Fax: 301-480-4368
e-mail: jz44m@nih.gov

Data Coordinating Center:

Patee Gesuwan
MSC 8505
2115 E Jefferson St.
Rockville, MD 20892
Phone: 301-443-6147
E-mail: gesuwanp@mail.nih.gov

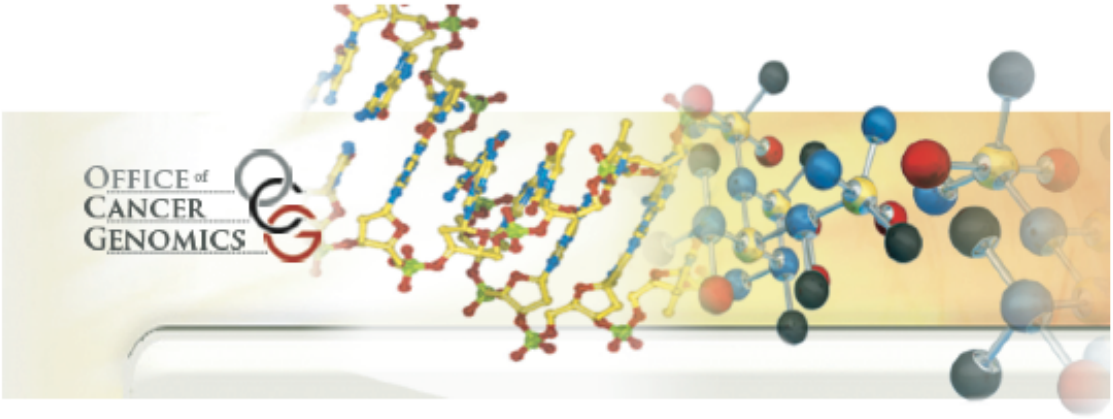
HTMCP Pathology Coordinator:

Peter B Illei, MD
Assistant Professor of Pathology
Director of Immunopathology Laboratory
Johns Hopkins Medical Institutions
401 N. Broadway, Weinberg Bldg. Rm. 2242
Baltimore, MD 21231
Tel: 410-502-5160
Fax: 410-614-9663
e-mail: pillei1@jhmi.edu

GSC-BC Coordinator:

Jacqueline Schein
Genome Sciences Centre
BC Cancer Agency
Suite 100
570 West 7th Avenue
Vancouver, BC V5Z 4S6
Canada
Email: jschein@bcgsc.ca
Phone: 604-877-6088

National Cancer Institute



BLGSP Protocols

U.S. DEPARTMENT
OF HEALTH AND
HUMAN SERVICES

National Institutes
of Health

Adopted:_____
2nd Version:_____
3rd Version:_____
Reviewed:_____
4th Version:_____

DOCUMENT REQUIREMENTS FOR SAMPLE SUBMISSION TO THE BURKITT LYMPHOMA GENOME SEQUENCING PROJECT

I. INTRODUCTION:

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Foundation for Burkitt Lymphoma Research have developed an initiative to establish a genomic databank to explore potential genetic changes in patients with Burkitt Lymphoma.

It is imperative that all personnel involved in the project read all the protocols and adhere to them at all times. It is your responsibility as a contributor to the BLGSP to familiarize yourself with all aspects of the procedures and assure their compliance.

A. SCOPE AND PURPOSE:

1. To list all the documents needed in order to start collection of samples for the Burkitt Lymphoma Genome Sequencing Project (BLGSP).
2. This protocol applies to all Tissue Source Sites (TSSs) providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times and which samples were affected. This information should be given within 48 hours of the occurrence to the project team by sending an e-mail to Dr. Robin S. Broughton (**robin.broughton@nih.gov)** with the details.

B. REQUIREMENTS:

1. Every TSS must have an IRB-approved protocol in place that allows collection of tumor tissue, matched normal tissue (blood, whenever possible) and clinical data that can be used in a characterization project. The protocol must have explicit language permitting the molecular characterization of the samples by genomic-scale methodologies, and subsequent deposition of the data into a public, but protected database.

2. Every patient accrued to the project must be enrolled in the protocol and agree to participate by signing an informed consent.
3. If you require assistance drafting such protocol or informed consent form, please contact the Project Team (PT) representative (address below). OCG has templates that contain the appropriate language.
4. TSSs must have in place a materials transfer agreement (MTA) with the Genome Science Center at British Columbia (GSC-BC, address below) to allow transfer of tissues and pathology reports. A sample MTA can be provided by the PT upon request.
5. OCG will store a copy of the IRB-approved protocol and a blank informed consent form. Additionally, certification that such protocol exists, and that patients have been consented, must be produced by the TSS Institution before the samples can be accepted and costs can be reimbursed. A template of such certification document can be found in Appendix A.
6. The completed Institutional certification must be sent to the PT before any sample can be shipped.

CONTACTS:

Project Team (PT) Representative:

Dr. Robin S. Broughton
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-3860
Fax: 301-480-4368
e-mail: robin.broughton@nih.gov

Data Coordinating Center:

Patee Gesuwan
MSC 8505
2115 E Jefferson St.
Rockville, MD 20892
Phone: 301-443-6147
E-mail: gesuwanp@mail.nih.gov

BLGSP Pathology Coordinator:

Dr. John Chan MD
Amelia and Austin Vickery Professor of Pathology
Co-Director, Center for Lymphoma and Leukemia Research
University of Nebraska
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7689
Fax: 402-559-6018
E-mail: jchan@unmc.edu

GSC-BC Coordinator:

Jacqueline Schein
Genome Sciences Centre
BC Cancer Agency
Suite 100
570 West 7th Avenue
Vancouver, BC V5Z 4S6
Canada
Email: jschein@bcgsc.ca
Phone: 604-877-6088

Adopted:_____
2nd Version:_____
3rd Version:_____
Reviewed:_____
4th Version:_____

PROCESSING TISSUE FOR MOLECULAR CHARACTERIZATION OF BURKITT LYMPHOMA TUMORS

I. INTRODUCTION

A. SCOPE AND PURPOSE:

1. To establish a procedure for tissue processing and storage by Tissue Source Sites (TSS).
2. This protocol applies to all TSS providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times, and which samples were affected. This information should be given within 48 hours of occurrence to the project team by sending an e-mail to Dr. Robin S. Broughton (**robin.broughton@nih.gov)** with the details.

B. SAFETY PRECAUTIONS:

1. Wear personal protective equipment (PPE) such as lab coats and gloves.
2. Liquid nitrogen is extremely cold and can cause 'burns'. Wear gloves that are specially made to withstand liquid nitrogen, eye protection (preferably Face Shield) and a lab coat to protect skin from splashes and spills. Liquid nitrogen is an asphyxiant; be sure to use in a well-ventilated area.
3. Acute overexposure to formaldehyde solutions and/or vapors causes severe eye, skin, and respiratory tract irritation.

C. EQUIPMENT AND MATERIALS:

1. Personal protective equipment (PPE) to include heavy duty gloves, eye protection (preferably Face Shield), lab coat and closed-toe shoes
2. Plastic cassette mold(s) for Formalin fixation.
3. Cryovials (e.g. 2mL vials from ChartBiomed, Part Number 10778828)
4. Freezer resistant labels with project-assigned ID (obtained from Project Team, see BLGSP SOP #003)
5. Dewar thermo-flask
6. Isopentane
7. Liquid Nitrogen
8. Formalin (10% solution)
9. Fine point Cryomarker (e.g. Nalge Nunc Cryomarker Black #6313-0020)

MARK ALL CONTAINERS WITH THE LABELS CARRYING PATIENT PROJECT-ASSIGNED ID OBTAINED PRIOR TO SURGERY.

II. PROCEDURE:

A. Tissue diagnosed as Burkitt Lymphoma should be processed as follows:

1. Wearing sterile gloves cut the tissue into multiple 2 mm thin sections using a sterile scalpel.
2. Place tissue into various containers as follows:
   i. **24-HOUR FORMALIN FIXATION**: Submit two representative tissue pieces for diagnosis, including 1-2 blocks to your Histology Lab. Tissue in formalin should be no more than 2 mm in thickness for proper fixation.
   ii. **FREEZING TISSUE**: Select two or three representative pieces of tissue measuring about 10 x 10 x 2 mm in dimension. Freeze as many pieces as possible. Do not freeze the tissue with Freon.
   Freeze the tissues as described below:

(i) Perform snap freezing of fresh tissue ASAP

1. It is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is ablated from patient.
2. Do not perform snap freezing with bare hands. Wear gloves at all times.

(ii) Set Up Freezing Station

1. Fill a small 100 ml metal beaker about 1/4 full with isopentane (2-methylbutane, certified grade).
2. Fill the Dewar thermo-flask about 1/3 full with liquid nitrogen.
3. Use extreme caution when dispensing liquid nitrogen

(iii)Label Cryovial As Needed

1. Use a cryomarker for labelling.
   a. Use a cryovial for tissue snap freezing.
   b. Label cryovial with freezer-resistant labels obtained prior to surgery (see BLGSP SOP #003).

(iv)Freezing Tissue in Cryovial

a. Cut a 1cm by 3 cm strip of histowrap

b. Put the tissue on the histowrap strip

c. Place the histowrap strip containing tissue into a labelled cryovial, using a pair of forceps.

d. Screw on the cap **tightly** or else isopentane will seep into the vial during freezing and create a liquid in the vial upon thawing.

e. Lower the 100 ml metal beaker containing isopentane half-way into the liquid nitrogen for cooling. The liquid nitrogen will boil as the beaker is lowered, when the isopentane is reaching its freezing

point the tone of the boiling will increase for 2-3 seconds.

f. Lift the beaker out of the liquid nitrogen once you see beads of solid isopentane at the bottom of the beaker (about 2 minutes).

g. Use long forceps to hold the cryovial down into the cooled isopentane. Hold for at least 1 minute.

h. Use the long forceps to take out the cryovial/ frozen tissue.

i. Store Frozen tissue vial(s) in Liquid Nitrogen Storage Tanks.

B. Make a gross report of the sample using the dictation template below.
C. Any questions regarding this protocol should be directed to the BLGSP Pathology Coordinators at 402-559-7689 or 402-559-7526.

THE FROZEN SPECIMENS SHOULD BE KEPT FROZEN ON DRY ICE AT ALL TIMES DURING TRANSPORT TO AND FROM STORAGE TANKS.

BLGSP STUDY GROSS DICTATION TEMPLATE

History:
The patient is a…

Source/Gross:
The specimen is received (**fresh vs. fixed**) in (**# containers**), each labeled with the project-assigned ID "#" and designated "#." The specimen consists of (**gross to include number of fragments, size, appearance, etc.**)

Specimens submitted are:

Fixed in formalin for 24 hours – (**size, # of pieces in each block, and cassette designation**)
Snap Frozen – (**size and # of blocks**)

CONTACTS:

BLGSP Pathology Coordinators:

Dr. John Chan MD
Amelia and Austin Vickery Professor of Pathology
Co-Director, Center for Lymphoma and Leukemia Research
University of Nebraska
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7689
Fax: 402-559-6018
E-mail: jchan@unmc.edu

OR

Dr. Kai Fu, MD, PhD
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7526
Fax: 402-559-6018
E-mail: kfu@unmc.edu

Project Team (PT) Representative:

Dr. Robin S. Broughton
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-3860
Fax: 301-480-4368
e-mail: robin.broughton@nih.gov

Adopted:_____
2nd Version:_____
3rd Version:_____
Reviewed:_____
4th Version:_____

PROSPECTIVE SAMPLE SUBMISSION PROCEDURE FOR THE BURKITT LYMPHOMA GENOME SEQUENCING PROJECT

I. INTRODUCTION:

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Foundation for Burkitt Lymphoma Research have developed an initiative to establish a genomic databank to explore potential genetic changes in patients with Burkitt Lymphoma.

A. SCOPE AND PURPOSE:

1. To establish a general procedure to inform personnel of all the steps necessary for a successful submission of a sample to the Burkitt Lymphoma Genome Sequencing Project (BLGSP).
2. This protocol applies to all Tissue Source Sites (TSSs) providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times, and which samples were affected. This information should be given within 48 hours of the occurrence to the project team (PT) representative by sending an e-mail to Dr. Robin S. Broughton (**robin.broughton@nih.gov)** with the details.

II. PROCEDURES:

A. BEFORE PATIENT ACCRUAL BEGINS:

1. Make sure all the documents required for sample shipment as spelled out in BLGSP SOP# 001 are in place before you start case accruals.

B. BEFORE PATIENT SURGERY:

1. Create a TSS-assigned ID for your patient. Your institution will be the keeper of the key as described in your approved IRB protocol.
2. Contact the data coordinating center (DCC, see address below) with your TSS-assigned ID to obtain a project-assigned ID to use in all documents regarding the case

and all materials shipped. **The TSS is responsible for maintaining the link between project-assigned ID and TSS-assigned ID in order to retrieve clinical information when required.** It is the TSSs responsibility to be able to track the patient's records back in the event that the original researcher(s) at the institution lose their affiliation.

3. Contact the PT and obtain forty (40) freezer-resistant labels that you should use to mark all containers/slides carrying materials for the project.
4. Make sure to prepare the tissue freezing station and have ready all the materials needed for tissue processing (BLGSP SOP# 002).
5. Inform the research nurse that a 10ml peripheral blood sample must be obtained from the patient to use as a non-tumoral control (see Appendix B). Store the blood sample in the refrigerator until processing (see BLGSP SOP# 004). Time in storage must be decided at site and reported back to Project Team.

C. DURING PATIENT SURGERY:

1. Inform the surgical staff of the tissue requirements for the project (see Appendix B).
2. Have a person ready to transport the ablated tissue to the processing station. It is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.

D. AFTER SURGERY:

1. Process solid tissue as described in the tissue processing protocol (BLGSP SOP #002). Timely processing is crucial, it is generally accepted that for the best tissue preservation snap freezing should take place within 20 minutes after tissue is obtained from the patient.
2. Process the blood sample according to protocol (see BLGSP SOP #004). Store isolated cells in liquid nitrogen storage until shipment.
3. Obtain eight to ten (8-10) unstained 4 μm sections from the formalin-fixed block. Affix one of the provided freezer-resistant labels to each slide.

E. PREPARING SAMPLES AND SHIPMENT:

1. Contact the GSC-BC coordinator to obtain a cryoport transport vessel to ship the cryovials containing frozen tumor sample sections and frozen blood cells.
2. Once the cryoport arrives follow the frozen sample shipment protocol (BLGSP SOP #006) and send the frozen samples to the GSC-BC. Upon shipping, provide both the GSC-BC and PT with tracking number.
3. Send the eight to ten (8-10) unstained 4 μm sections obtained from the formalin fixed blocks to the pathology coordinator at the University of Nebraska (see address below). On shipment, provide both the pathology coordinator and PT with tracking

number. For shipment use a closable box (such as Thermo Scientific* Plastic Slide Box, capacity 25 slides, catalog# B1780).

4. Collect all the clinical data requested in the sample requirements (Appendix B) and send electronically to the DCC.

NOTES:

- A checklist is provided to help you track all the steps required by this process (Appendix C). Please use it!
- If any one of the required items (institutional certification, confirmation of informed consent, frozen tissue, frozen blood cells, unstained slides and clinical data) are not present, the submission is incomplete and reimbursement of costs cannot proceed.
- **At no point in the process can traditionally-used identifying information (such as the patient name, address, phone number, medical record number, or social security number) be used to label samples. Only use the project-assigned ID and labels provided by the Project Team.**

CONTACTS:

Project Team Representative:

Dr. Robin S. Broughton
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-3860
Fax: 301-480-4368
E-mail: robin.broughton@nih.gov

Data Coordinating Center:

Patee Gesuwan
MSC 8505
2115 E Jefferson St.
Rockville, MD 20892
Phone: 301-443-6147
E-mail: gesuwanp@mail.nih.gov

BLGSP Pathology Coordinators:

Dr. John Chan MD
Amelia and Austin Vickery Professor of Pathology
Co-Director, Center for Lymphoma and Leukemia Research
University of Nebraska
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7689
Fax: 402-559-6018
E-mail: jchan@unmc.edu

OR

Dr. Kai Fu, MD, PhD
Department of Pathology

UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7526
Fax: 402-559-6018
E-mail: kfu@unmc.edu

GSC-BC Coordinator:

Jacqueline Schein
Genome Sciences Centre
BC Cancer Agency
Suite 100
570 West 7th Avenue
Vancouver, BC V5Z 4S6
Canada
Email: jschein@bcgsc.ca
Phone: 604-877-6088

APPENDIX A: <u>Template of Institutional Certification</u>

[This Institutional Certification should be submitted on the PI's institutional letterhead.]

Date: Month Day, Year

To: Elizabeth Gillanders, Ph.D.
Branch Chief and NCI Data Access Committee Chair
National Institutes of Health
MSC 7324
6130 Executive Blvd
Rockville, MD 20892

Re: Certification of [name of PI's institution] to Accompany Submission of the Dataset for the HMP Demonstration Project, [insert name of Project] to the NIH Database of Genotypes and Phenotypes (dbGaP).

Dear Dr. Gillanders:

[Name of PI's institution] adheres to the *Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS),* Notice Number: NOT-OD-07-088. [Name of PI's institution] provides the following Certification in regard to the Dataset for the [name of Project], which is being deposited into dbGaP.

- The data submission is consistent with all applicable laws and regulations, as well as institutional policies.

- All uses of these data that are deemed acceptable and approved per NIH policy and that follow the dbGaP procedures for access are allowable, with the following restriction:

  These data may be used for general scientific research by qualified investigators that are performing research projects and that have likely relevance to developing more effective treatments, diagnostic tests, or prognostic markers, including cancer research.

- The identities of research participants will not be disclosed to dbGaP

- An Institutional Review Board has reviewed and verified that:

  - The submission of data to dbGaP and subsequent sharing for research purposes are consistent with the informed consent of the study participants from whom the data were obtained;

- The plan for de-identifying datasets is consistent with the standards outlined in NOT-OD-07-088;
- [Name of institution] has considered the risks to the individuals, their families, and groups or populations associated with data submitted to dbGaP and determined risks to be reasonable in relation to anticipated benefits to society; and
- The phenotype data to be submitted were collected in a manner consistent with 45 CFR Part 46. .

The suggested Acknowledgement Statement to accompany the data set is:

Acknowledgement Statement

This project has been funded in whole or in part with Federal funds from the National Cancer Institute, National Institutes of Health, under XXXXXXXXX.

If additional information is required, please do not hesitate to contact us.

Sincerely,

[Need signatures from both the signing official at the PI's institution and the PI for the Project.]

APPENDIX B: Sample Requirements

Burkitt Lymphoma Genome Sequencing Project
Tissue Sample Requirements for Accrual

Tissue Requirements:

To be accepted to the project, the following conditions have to be met at the tissue level.

- Paired tumor and normal (non-involved tissue or blood) must be available in sufficient quantities (~100mg of frozen tumor tissue and 10ml of blood).
- Tissues (both normal and tumor) need to be snap frozen. Time between tissue extraction and freezing must be recorded.
- Optimal storage of the tissues is in N_2(liq), but -80ºC or lower is acceptable. The form of tissue storage must be recorded.
- There must be enough tissue of both to produce a 4µm thick section from the top for H&E staining, then 8-10 sections of 20µm thickness, followed by another 4µm section to stain by H&E. **The number of sections needed is based on a block with a surface area of about one square cm. If the area is smaller, proportionately more sections will be required.**
- Tumors need to have a minimum percent of tumor nuclei between 70-80% as assessed on an H&E section physically adjacent to the specimen that is candidate for generating the RNA and DNA.
- A paraffin embedded block for pathology consensus review must exist for the tumor.

Burkitt Lymphoma Genome Sequencing Project
Clinical Data Requirements for Accrual

Clinical Data Requirements:

To be accepted to the project, the following conditions must be met at the clinical data level. The samples must meet ALL the clinical data elements (CDEs) here listed.

These clinical data elements must be reported to the DCC as an initial report within two weeks of enrolling the patient. Updates must be sent to the DCC as the patient returns for periodic visits (ideally every 3-4 months).

- Patients need to be consented in such a way that allows for the use of their tissues for genomic-scale molecular characterization.

Data element	Data type	Example
Unique identifier	text	XX-XXXX
WHO diagnosis	text	BL
Date pathologic diagnosis	date (dd.mm.yyyy)	01.02.2003
Age at diagnosis	number	55
Gender	text	M
Race + Ethnicity (2 CDEs, CDC/Census std)		
Stage (Ann Arbor)	text	4A
Performance status (ECOG)	text	1
Lactate dehydrogenase level (LDH) (as ratio of measured value/upper limit of normal)	number	1.3
Sites of extranodal disease	text	bone marrow, lung
Maximum tumor bulk (cm)	number	8
Anatomic site of maximum tumor bulk	text	bone marrow, lung
Primary treatment	text	CHOP-R
Primary treatment start date		
Response to primary treatment	text	Complete
Date of assessment of response		
Date progressive disease, if occurred	date (dd.mm.yyyy)	11.11.2005

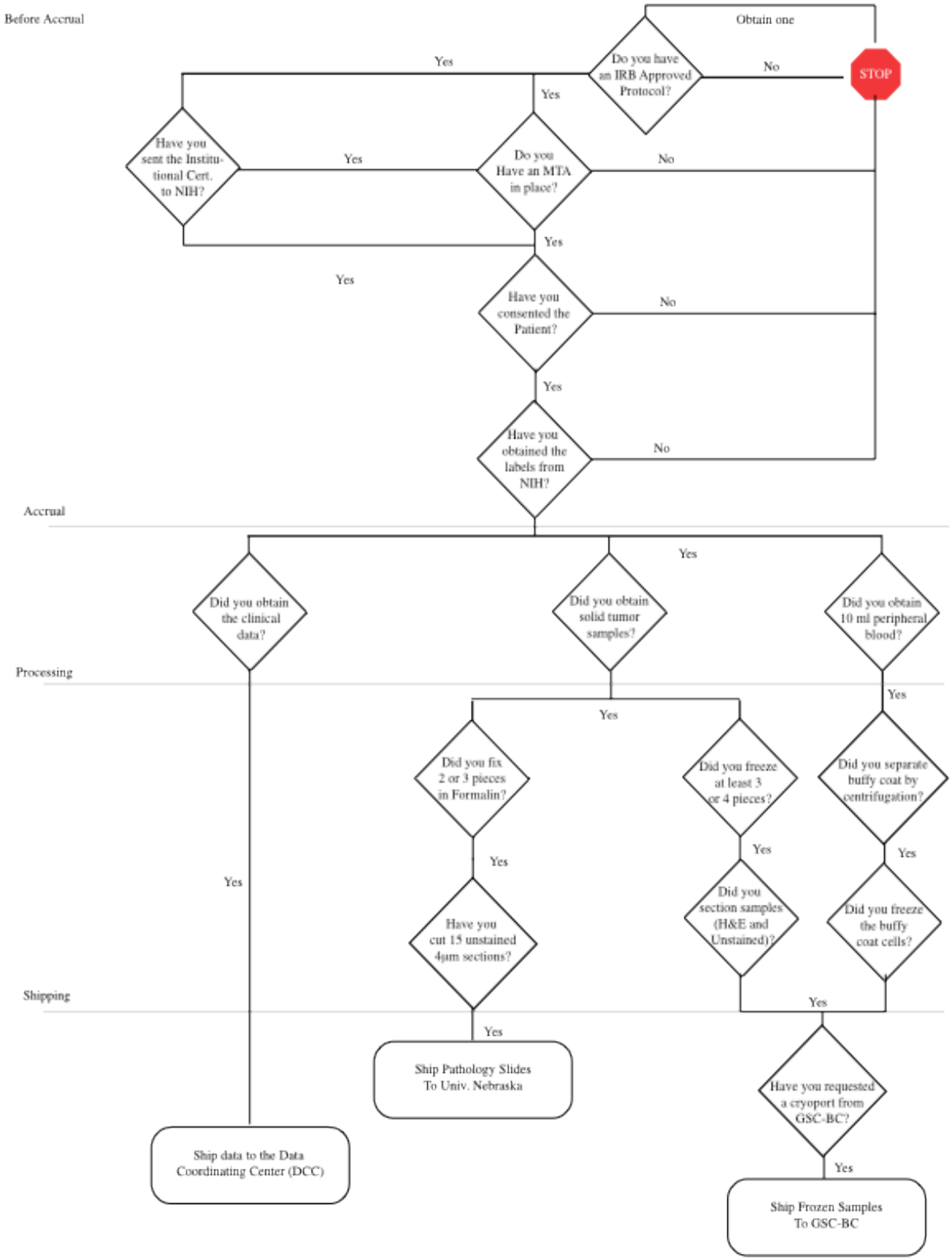
Primary site of progression	text	Lung
Secondary treatment	text	GDP
Secondary treatment start date		
Hematopoietic stem cell transplant (HSCT) (yes/no)	text	Yes
Date HSCT	date (dd.mm.yyyy)	03.01.2006
Malignant cells in bone marrow histology (yes/no)	text	Yes
Surface antigens, IHC, CD		
HIV status (pos/neg)	text	Negative
EBV status of malignant cells (EBER) (pos/neg)	text	Positive
Date last follow-up	date (dd.mm.yyyy)	11.11.2006
Status at last follow-up (alive/dead)	text	Alive
Number of months from diagnosis to last follow-up (living patients only)	number	
Cause of death	text	lymphoma
Date of death	date (dd.mm.yyyy)	05.24.2009

APPENDIX C: Checklist of Task Completion for Sample Submission

Date:
Institution:
Operator:

- Do you have an IRB approved protocol?
- Have you consented the patient?
- Have you sent your Institutional Certification to the Project Team?
- Have you obtained the project-assigned ID and labels from the Project Team?
- Do you have frozen sections in cryovial and H&E stained slides? Are they labeled?
- Do you have frozen blood cells? Are they correctly labeled?
- Have you secured a cryoport from the Genome Science Center at British Columbia?
- Do you have (15) unstained 4 μm sections from the Formalin-fixed block? Are they labeled?
- Do you have the clinical data elements required by the Project? (Appendix B)

ONLY if all the above items check out, you are ready to ship the samples.


Before Accrual
Obtain one
Do you have an IRB Approved Protocol?
Yes
No
STOP
Yes
Have you sent the Institutional Cert. to NIH?
Yes
Do you Have an MTA in place?
No
Yes
Yes
Have you consented the Patient?
No
Yes
Have you obtained the labels from NIH?
No
Accrual
Yes
Did you obtain the clinical data?
Did you obtain solid tumor samples?
Did you obtain 10 ml peripheral blood?
Processing
Yes
Yes
Did you fix 2 or 3 pieces in Formalin?
Did you freeze at least 3 or 4 pieces?
Did you separate buffy coat by centrifugation?
Yes
Yes
Yes
Yes
Did you section samples (H&E and Unstained)?
Did you freeze the buffy coat cells?
Have you cut 15 unstained 4µm sections?
Shipping
Yes
Yes
Yes
Ship Pathology Slides To Univ. Nebraska
Have you requested a cryoport from GSC-BC?
Ship data to the Data Coordinating Center (DCC)
Yes
Ship Frozen Samples To GSC-BC

Adopted:_____
2nd Version:_____
3rd Version:_____
Reviewed:_____
4th Version:_____

PROCESSING BLOOD SAMPLES FOR THE BURKITT LYMPHOMA GENOME SEQUENCING PROJECT

I. INTRODUCTION:

The National Cancer Institute's Office of Cancer Genomics (OCG) and the Foundation for Burkitt Lymphoma Research have developed an initiative to establish a genomic databank to explore potential genetic changes in patients with Burkitt Lymphoma.

A. SCOPE AND PURPOSE:

1. To establish a common procedure for blood processing previous to shipment to the Genome Science Center at British Columbia (GSC-BC) by tissue source sites (TSS).
2. This protocol applies to all TSSs providing tissues prospectively.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times, and which samples were affected. This information should be given within 48 hours of occurrence to the project team by sending an e-mail to Dr. Robin S. Broughton (**robin.broughton@nih.gov)** with the details.

B. SAFETY PRECAUTIONS:

1. Wear personal protective equipment (PPE) such as lab coats and gloves.

C. EQUIPMENT AND MATERIALS:

1. Personal protective equipment (PPE) to include heavy duty gloves, eye protection (preferably Face Shield), lab coat and closed-toe shoes
2. Clinical Centrifuge
3. Red Blood Cell (RBC) Lysis Buffer (0.15 M NH_4Cl, 10 mM $KHCO_3$, 0.1 mM EDTA in dH_20, 0.2 μm filtered)
4. Freezing Media (10% DMSO, 20% FCS, RPMI 1640)
5. Conical tubes (e.g. 15 and 50 ml polypropylene tubes from BD Biosciences, Part Numbers 352097 and 352098, respectively)
6. Cryovials (e.g. 2mL vials from ChartBiomed, Part Number 10778828)
7. Freezer resistant labels with project-assigned ID (obtained from Project Team, see BLGSP SOP #003)
8. Dewar thermo-flask
9. Liquid nitrogen
10. Isopentane (2 methyl butane)

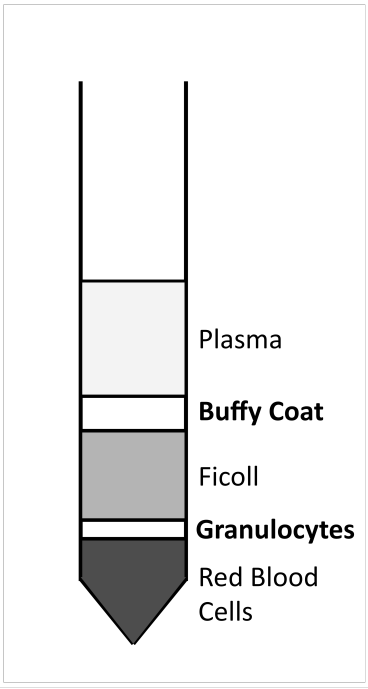
MARK ALL CONTAINERS WITH THE LABELS CARRYING PATIENT PROJECT-ASSIGNED ID OBTAINED PRIOR TO SURGERY.

II. PROCEDURE:

A. Collect 10 ml of blood in tubes containing anticoagulant (e.g. heparin (green top), EDTA (lavender top), or ACD (yellow top)). If there is indication that **tumor cells are present in blood,** fractionate the blood as soon as possible after collection (see section B). If fractionation is not needed, then red cell lysis with collection of all the nucleated calls is sufficient.

B. **Blood Separation**:

1. In a 50 ml conical tube, dilute 10 ml of the whole blood with 40 ml of buffer.
2. To a 50 ml conical tube, add 15 ml of Ficoll. Carefully layer 30 ml of the diluted blood over the Ficoll.
3. Fractionate the diluted blood by centrifuging at 400 *X* g for 30 min at room temperature with the brake off. This will separate the blood into three prominent layers: an upper plasma layer, a middle Ficoll layer, and a lower red blood cell (RBC) layer. At the interface between the plasma layer and the Ficoll layer there will be a thin layer containing the white blood cells (WBCs) / buffy coat and between the Ficoll and RBC layer a thin interface containing the granulocytes (see Figure). **NOTE:** In a typical clinical centrifuge 1500-2000 *X* g i*s* ~800 rpm. Check the appropriate settings for your centrifuge using the nomogram in your user's manual.



4. Use a disposable, plastic transfer pipet (e.g. Falcon Cat #357524) to aspirate off the plasma (upper layer) down to ~1 mm from the buffy coat (see Figure). Discard the plasma into a container with bleach When removing the plasma do not disturb the WBC layer, also called the buffy coat, which forms a thin film between the upper plasma layer and the lower layer of packed RBCs. Samples with exceptionally high WBC counts will have a thicker buffy coat.
5. Recover the WBCs in ≤0.5 ml with a 1 ml pipetman. Do not take too much Ficoll (the layer below the buffy coat), as it is toxic to cells. Estimate the volume recovered and write the information into the datasheet.
6. Place the recovered buffy coat into a freezer-resistant labeled cryovial cooled on ice. Labels are obtained prior to surgery from the Project Team (BLGSP SOP #003). Screw on the cap **tightly** to prevent isopentane from seeping into the vial during freezing as it creates a liquid in the vial upon thawing.

7. Aspirate off the Ficoll layer carefully into an Erlenmeyer flask with bleach (see Figure) taking care not to disturb the granulocyte layer between the Ficoll layer and the pelleted RBCs. The granulocytes sit on the surface of the RBCs and are visible as a white haze. Discard the Ficoll.
8. Recover the granulocytes, usually the volume is ~ ≤0.5 ml, using a 1 ml pipetman. Place cells into a labeled 15 ml conical tube.
9. Add 1 ml of the RBC Lysis Buffer to the granulocytes and incubate at room temperature for 5-10 min.
10. Centrifuge the granulocytes at 300 *X* g for 10 min at room temperature with the brake on.
11. Aspirate and discard the supernatant (~1.5 ml) and re-suspend the granulocyte cell pellet in 0.5 ml of Freezing Media by gently pipetting up and down.
12. Place the recovered granulocytes into a cooled freezer-resistant labeled cryovial. Labels can be obtained from the Project Team (BLGSP SOP #003). Screw on the cap **tightly** to prevent isopentane from seeping into the vial during freezing.

C. Set Up Freezing Station

1. Fill a small 100 ml metal beaker about 1/4 full with isopentane (2-methylbutane, certified grade).
2. Fill the Dewar thermo-flask about 1/3 full with liquid nitrogen.
3. Use extreme caution when dispensing liquid nitrogen.

D. Freezing Blood Cells in Cryovials

1. Using long forceps lower the 100 ml metal beaker containing isopentane half-way into the liquid nitrogen for cooling. The liquid nitrogen will boil as the beaker is lowered, when the isopentane is reaching its freezing point the tone of the boiling will increase for 2-3 seconds.
2. Lift the beaker out of the liquid nitrogen once you see beads of solid isopentane at the bottom of the beaker (about 2 minutes).
3. Use long forceps to hold the cryovial down into the cooled isopentane. Submerge cryovial for at least 1 minute.
4. Take out the cryovial containing frozen tissue.
5. Store frozen tissue vial(s) in liquid nitrogen storage tanks or -80ºC Freezers.

E. Any questions regarding this protocol should be directed to the BL Pathology Coordinators at 402-559-7689 or 402-559-7526.

THE FROZEN SPECIMENS SHOULD BE KEPT FROZEN ON DRY ICE AT ALL TIMES DURING TRANSPORT TO AND FROM STORAGE TANKS.

CONTACTS:

BLGSP Pathology Coordinators:

Dr. John Chan MD
Amelia and Austin Vickery Professor of Pathology
Co-Director, Center for Lymphoma and Leukemia Research
University of Nebraska
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7689
Fax: 402-559-6018
E-mail: jchan@unmc.edu

OR

Dr. Kai Fu, MD, PhD
Department of Pathology
UMA Bldg, Rm 3528, Zip 3135
University of Nebraska Medical Center
668 S. 41st Street
Omaha, NE 68105
Phone: 402-559-7526
Fax: 402-559-6018
E-mail: kfu@unmc.edu

Project Team (PT) Representative:

Dr. Robin S. Broughton
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-3860
Fax: 301-480-4368
e-mail: robin.broughton@nih.gov

Adopted:_____
2nd Version:_____
3rd Version:_____
Reviewed:_____
4th Version:_____

SAMPLE SHIPPING GUIDELINES FOR THE BURKITT LYMPHOMA GENOME SEQUENCING PROJECT

I. INTRODUCTION:

Tumor samples from Burkitt Lymphoma patients are rare and they may be accrued at specific tumor source sites (TSS) at a rate of 3-5 per calendar year. Some tumor samples may also be HIV-infected. Shipping costs for infectious labeled material in vapor phase liquid nitrogen containers (cryoports) are expensive.

A. SCOPE AND PURPOSE:

1. To establish a sample shipping guideline standard to be applied to all samples contributed to the Burkitt Lymphoma Genome Sequencing Project (BLGSP) that balances the need for expeditious transport while maintaining cost efficiency.
2. This procedure applies to all TSSs.

II. ADOPTED STANDARD:

- Immediate requests for a cryoport will be made to the Genome Science Center at British Columbia (GSC-BC) coordinator when the contributing TSS has in its possession 3 or more matched tumor-normal tissues.
- However, if less than three cases are accrued, and the date of oldest sample resection is more than 4 months, shipment of this/these sample(s) is warranted.

Any questions regarding this protocol should be directed to Dr. Robin S. Broughton at 301-451-3860.

CONTACTS:

Project Team Representative:

Dr. Robin S. Broughton
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-3860
Fax: 301-480-4368
E-mail: robin.broughton@nih.gov

GSC-BC Coordinator:

Jacqueline Schein
Genome Sciences Centre
BC Cancer Agency
Suite 100
570 West 7th Avenue
Vancouver, BC V5Z 4S6
Canada
Email: jschein@bcgsc.ca
Phone: 604-877-6088

Adopted:_____
2nd Version:_____
3rd Version:_____
Reviewed:_____
4th Version:_____

SHIPPING CRYOPORTS CONTAINING FROZEN BIOSAMPLES FOR PROCESSING AND EXTRACTION OF NUCLEIC ACIDS

I. INTRODUCTION:

Cryoports are shipped from the Genome Sciences Center at the British Columbia Cancer Agency (GSC-BC) to the Tissue Source Site (TSS). TSSs are instructed to use this SOP when shipping samples to the GSC-BC.

A. SCOPE AND PURPOSE:

1. To establish a procedure for personnel in shipping the cryoports.
2. This procedure applies to all laboratory personnel.
3. Any deviation from this protocol should be noted in the lab notebook, indicating nature of deviation, times and samples affected. This information should be given immediately to the project team by sending an e-mail to Dr. Robin S. Broughton (**robin.broughton@nih.gov)** with the details.

B. SAFETY PRECAUTIONS:

1. Wear personal protective equipment (PPE) such as lab coats and gloves.
2. Liquid nitrogen is extremely cold and can cause 'burns'. Wear gloves that are specially made to withstand liquid nitrogen, eye protection and a lab coat to protect skin from splashes and spills. Liquid nitrogen is an asphyxiant; be sure to use in a well-ventilated area.
3. Always keep the cryoport in the upright position.

C. EQUIPMENT AND MATERIALS:

1. Cryoport, obtained in 3 or 4 days in advance from the GSC-BC Coordinator (see below).
2. Personal protective equipment (PPE) to include heavy duty gloves, eye protection (preferably Face Shield), lab coat and closed-toe shoes
3. Shipping documents

II. PROCEDURE:

1. Request cryoport from GSC-BC shipping coordinator 3-4 days in advance of sectioning samples.
2. Complete the appropriate shipping forms needed for the sample(s).
3. Complete the sample shipping document with the project-assigned ID obtained prior to surgery, the sample type information and any comments. Sign and date the form and have a second individual verify the contents of the shipment and sign and date the form.
4. Don personal protection equipment.
5. Open the cryoport shipping vessel and remove the temperature probe that has been wrapped in bubble wrap and placed between the cryoport and the outside shipping vessel. Lift the cryoport out of the shipping vessel to access the data logger which has also been wrapped in bubble wrap and placed between the cryoport and the shipping vessel.
6. Open cryoport lid carefully.
7. Take the temperature of the cryoport prior to placing the samples in the cryoport.
    a. Turn the On/Off switch on the digital thermometer to the "On" position.
    b. Press the Celsius/Fahrenheit to read "C" in the upper right corner of the temperature screen.
    c. Place the temperature probe into the cryoport for a minimum of five minutes.
    d. After five minutes, record the temperature of the cryoport on the Cryoport Temperature Log that is enclosed in the plastic tie envelope.
    e. If the temperature is -170°C or colder, it can be used to ship the samples to the GSC-BC. Place your samples in the cryoport and place the lid on the shipper and use one of the plastic ties to secure the lid. ALERT: If the temperature is warmer than -170°C, please contact the GSC-BC coordinator for instructions.
    f. Wrap the data logger and temperature probe and return all items to the shipping vessel in reverse order as listed above.
8. Carefully close the lid. Affix a plastic zip tie through the loop of the lid and the loop on the cryoport.
9. Place all shipping documents, including the Sample Shipping Document and the Cryoport Temperature Log, into the plastic sleeve.
10. Notify the shipping carrier for pick-up. Under normal conditions, shipments should only be sent to GSC-BC on Monday through Wednesday. If an exception is needed, the GSC-BC must be contacted at 604-877-6088 for further instructions and to alert the GSC-BC personnel of any schedule changes.
11. Attach the enclosed Federal Express shipping label to the handle of the outside shipping vessel and use the other enclosed plastic tie to secure the outside lock before returning the cryoport to GSC-BC.
12. TSS personnel will notify the coordinator by email stating the cryoport is being returned with tissue samples back to the GSC-BC.
13. The GSC-BC Coordinator will track the cryoport in transit.

14. If there are any exceptions to the normal shipping schedule or in the event of an anticipated shipment delay, the Coordinator will notify the GSC-BC on-call personnel of the potential arrival of samples after normal working hours or on the weekend.
15. Upon receiving the cryoport, the temperature will be recorded and quality control verified by a second individual.
16. Any questions regarding shipments to the GSC-BC should be directed to the GSC-BC Coordinator at 604-877-6088.

CONTACTS:

GSC-BC Coordinator:

Jacqueline Schein
Genome Sciences Centre
BC Cancer Agency
Suite 100
570 West 7th Avenue
Vancouver, BC V5Z 4S6
Canada
Phone: 604-877-6088
email: jschein@bcgsc.ca

Project Team (PT) Representative:

Dr. Robin S. Broughton
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-3860
Fax: 301-480-4368
e-mail: robin.broughton@nih.gov

Adopted:_____
2nd Version:_____
3rd Version:_____
Reviewed:_____
4th Version:_____

SAMPLE IDENTIFIER STANDARDS FOR THE BURKITT LYMPHOMA GENOME SEQUENCING PROJECT

I. INTRODUCTION:

To assure the privacy of all human subjects that have consented to donate their tissues and clinical data to the Burkitt Lymphoma Genome Sequencing Project (BLGSP), all the materials given to the project must be de-identified prior to shipment and study. This project-assigned ID must have a rational structure that permits tracking of which subproject, tissue source site (TSS) and case is labeled.

A. SCOPE AND PURPOSE:

1. To establish a sample identifying standard to be applied to all samples and data contributed to the BLGSP.
2. This procedure applies to all laboratory personnel.

II. ADOPTED STANDARD:

- Samples contributed to the BLGSP must be labeled with an ID obtained from the Data Coordinating Center (DCC) by the TSS previous to shipment.
- These code must have the following form:

BLGSP - ### - ##### - ##X - X

Where:

1. BLGSP stands for Burkitt Lymphoma Genome Sequencing Project
2. The next three digits identify the Tissue Source Site
3. The next five digits are the sample identifier
4. The last two digits specify sample type (01=Tumor, 10=Normal; 20=diagnostic update pathology report; 50=consensus pathology report)
5. The first letter identifies the aliquot/section of the sample.
6. The last letter identifies nucleic acid type (R=RNA, D=DNA)

Any questions regarding this protocol should be directed to the Project Team (PT) representative Dr. Robin S. Broughton at 301-451-3860.

Adopted:_____
2º Version:_____
3º Version:_____
4º Version:_____
Under Revision:_____

VERY USEFUL INSTRUCTIONS ON HOW TO COMPLETE A STUDY PROTOCOL REQUEST TO THE INSTITUTIONAL REVIEW BOARD (IRB) FOR THE BURKITT LYMPHOMA GENOME SEQUENCING PROJECT

INTRODUCTION:

The Burkitt Lymphoma Genome Sequencing Project's (BLGSP) goal is to develop a genomic databank of the molecular changes in Burkitt Lymphoma that will be available to the research community world-wide. It will allow the comparison between the cancer-related alterations in patients with Burkitt Lymphoma and those without. The project aims to generate large scale, high-quality data on the cancers' genomes and transcriptomes using 2nd and 3rd generation sequencing technology which means that the changes identified will include large genomic rearrangements, expression profile changes and detection of mutations.

In order for cases to be included in the project, the patients must provide consent of participation in an approved IRB protocol specifying that the samples can be used for genomic characterization and that the data deposited in a publicly available, yet patient privacy designed database. The Office of Cancer Genomics (OCG) of the National Cancer Institute has created a generic template that contains the appropriate language to help the Tissue Source Site (TSS) in producing the IRB document. This template lacks details that are Institution-specific and should not be considered complete.

SCOPE AND PURPOSE:

- To establish a set of instructions allowing each TSS to create their own IRB protocol to contribute samples to the BLGSP.
- These instructions should be useful to every TSS contributing samples to the BLGSP.

INSTRUCTIONS:

1. Obtain the IRB protocol template from either the SOP package sent when you agreed to participate in the BLGSP or the SharePoint site (https://ocg-sps.nci.nih.gov/Burkitt_Lymphoma/default.aspx). You may also request a copy from the project team (see address below).
2. Fill in your organization name, PI's name and other pertinent information in the form. The Project name should be "Burkitt Lymphoma Genome Sequencing Project" and its acronym is BLGSP.

3. The project rationale can be found in the introductory section above.
4. The total number of samples that will be analyzed is 120.
5. Details on amount of tissue requested is in BLGSP SOP #003 under the sample requirement section (page 8)
6. Details on the blood collection for germline DNA extraction can be found in BLGSP SOP #004.
7. All the operational details of the project are clearly specified in the SOPs sent to the TSSs. It is expected that all participating personnel will read the SOPs, be familiar with the project procedures and requirements and follow them in all instances.

Should you have any question please contact Dr. Broughton at 301-451-3860

Project Team Representative:

Dr. Robin S. Broughton
Office of Cancer Genomics
National Cancer Institute
31 Center Drive, Suite 10A07
Bethesda, MD 20892
Phone: 301-451-3860
Fax: 301-480-4368
e-mail: robin.broughton@nih.gov

Protocol 009 : BLGSP Pathology Review

is in Development